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OBSERVATIONS OF ANTISTREPTOLYSIN-O, C-REACTIVE PROTEIN AND ELECTROPHORETIC PROTEIN PATTERNS IN MATERNAL AND NEONATAL SERA

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THE desire to understand the dynamics of neonatal immunity is of long standing and has led to many studies concerning the transfer of immune bodies from mother to infant, the earliest of which was made by Kuttner and Ratner in 1923.[1] More recently the subject was reviewed and further developed by Osborn and others,[2] and the mechanism of the placental transmission of antibodies discussed by Cohen.[3]

The frequency of staphylococcic infections in the newborn is well known to all clinicians. The question arises as to whether the much lesser frequency of hemolytic streptococcal infections is due to its rarity in the environment of the newborn, or to the baby's immunity to such infections. With this view in mind, and with the hope of furthering our knowledge concerning the newborn infant's potential immunity to the streptococcus, we attempted this study. The purpose of our study was threefold, namely, to analyze the comparative titers of antistreptolysin-O in mother and infant; to make an independent survey of the relative presence or absence of C-reactive protein; and to determine by electrophoresis which of the protein fractions of these sera was involved in each test.

There are certain limitations to tests for immunity to the streptococcus. An elevated antistreptolysin-O titer has been commonly accepted as an index of immune response. However, even here, Hamburger and Lemon[4] showed that elevated antistreptolysin titers to type 19, group A infections did not protect against infections of type 17 streptococci. With these reservations, the relation between maternal and neonatal antistreptolysin levels has been used as a general indication of transferral of these substances across the placental membrane. Several authors[5-9] have reported the fetal antistreptolysin titers to be equal or higher than that of the maternal circulation. A group of authors from Stockholm[7]

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presented a summary of work on antistreptolysin titers in mothers, babies, and fetuses. They were able to demonstrate the existence of fetal antistreptolysin in low concentrations in the sixteenth and twenty-second week of gestation, lower than that of the mothers, and showing that a premature infant born at 30 to 39 weeks already has a titer closely corresponding with that of the mother.

C-reactive protein is an abnormal protein found in acute phase sera and was first described by Tillet and Francis,[10] subsequently by others.[11] Its presence may indicate a response to an inflammatory condition, to proliferative activity, or to an apparently noninfectious stimulus; for example, it may be found in late pregnancy,[12] in newborn infants with bacterial diseases,[13] and in subclinical bacterial infections. Apparently this substance is not the usual type of antibody; it is nonspecific toward the agent and fails to react in the absence of calcium.[10, 11]

Electrophoretic patterns of the serum proteins in newborn infants and their mothers were reported early by Moore and others,[14] and later by Kuhns and Hyland[15] and Oberman and others.[16] In our study we had hoped to elucidate the relation of gamma globulin to the formation of antibodies, and our electrophoretic analysis may be studied from this standpoint.

MATERIALS AND METHODS

The subjects of study were 44 apparently normal mothers and their newborn infants, all born by normal full-term deliveries.* The majority of patients in this series were of Puerto Rican extraction. All maternal and neonatal venous blood was drawn between the first and fourth post-partum days. Fourteen of the 44 specimens of infants' blood were taken from the cord, and the remaining 30 specimens were obtained by femoral vein puncture. Our three investigations were carried out simultaneously on the same specimens of sera.

The serum C-reactive protein (CRP) was determined on fresh serum by the method of Anderson and McCarty[17] using commercial antiserum.* The serum was incubated with the antiserum in capillary tubes for two hours at 37° C. followed by overnight refrigeration. The results were graded in millimeters of precipitate.

The antistreptolysin-O titer (ASLT) was determined by the method of Rantz and Randall[18] and expressed in Todd units. In this investigation a modification of the above method was employed in that the serum was immediately separated from the cells and frozen to prevent possible increase in titer due to bacterial contamination.[19]

Electrophoresis was carried out in duplicate on Whatman No. 3 paper, using Durrum's hanging strip method.[20] A sodium diethyl barbiturate (barbital) buffer of pH 8.6 and ionic strength 0.07 was used. After heat denaturation of the protein for 30 minutes, the strips were stained with bromphenol blue for 16 hours,[21] exposed briefly to ammonia fumes for color fixation, and read in a Spinco Analytrol. The latter is a combined photometer and automatic integrator. It measures and records the light absorption of the stained paper strip while producing a saw-toothed pattern

*Mothers and newborns were patients of Gouverneur Municipal Hospital, New York.

*Schieffelin & Co.

which represents the area under the recorded curve. The percentage of each fraction may thus be calculated. If the total protein is chemically determined, each fraction may be quantitated by percentage calculation. Prolonged exposure to light was avoided.[21] A control specimen was run concurrently and in duplicate on serum from a normal subject. A sample tracing with its analysis is shown in Fig. 1.

torting the percentage composition of protein fractions. It therefore became apparent that an occasional source of error in electrophoresis may be the use of hemolyzed specimens.

RESULTS

The ASLT of the paired mother-infant sera are shown in Table I, and it can be seen that a higher level was found in the infant. The arithmetic means ASLT for the 44 parturient

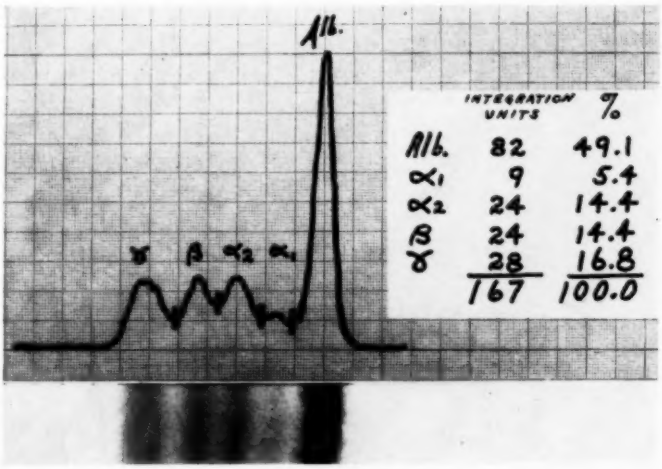

Fig. 1.—Electrophoretic pattern of the serum proteins of a normal parturient mother.

Grossly hemolyzed specimens were excluded from this series; therefore many cord blood specimens were discarded. Although hemolysis did not interfere with the CRP tests, it did interfere with the reading of the other two tests. In a few instances, slightly hemolyzed sera were used because the visible hemolysis was diluted before the significant readings were made. Early in our electrophoretic studies we discovered that the presence of hemolysis in serum deposited a hemoglobin band at the beta fraction, thereby dis-

women was 71.5, and for their infants was 91.2. Tabulating the difference in titer between mother and child gives the following figures:

	Total
Infant's titer higher	22 (49 per cent)
Infant's and mother's titer equal	17 (40 per cent)
Mother's titer higher	5 (11 per cent)

Fig. 2 plots the ASLT of unrelated mothers and infants, and illustrates the predominance of higher titers in infants. It can also be observed that among both groups of patients, three fourths of the titers were 100 units or

TABLE I. ANTISTREPTOLYSIN-O TITER (ASLT) AND C-REACTIVE PROTEIN (CRP) IN MOTHERS AND THEIR RESPECTIVE INFANTS

CASE NO.	MOTHER		INFANT			
			CORD		VENOUS	
	ASLT	CRP	ASLT	CRP	ASLT	CRP
1	12	0	12	0		
2	65	0	65	0		
3	12	1+	50	0		
4	50	1+	65	0		
5	65	2+	65	0		
6	65	1+	65	0		
7	12	3+	80	±		
8	65	3+	65	1+		
9	125	0	65	0		
10	50	1+	50	0		
11	50	1+	166	0		
12	166	0	100	±		
13	100	3+	167	0		
14	33	3+	33	0		
15	50	2+			125	1+
16	100	1+			100	±
17	50	2+			125	0
18	50	3+			50	±
19	100	2+			50	±
20	50	1+			100	1+
21	50	3+			100	±
22	>250	1+			50	1+
23	50	3+			100	0
24	12	±			12	3+
25	12	0			12	2+
26	125	0			166	0
27	125	2+			125	±
28	100	2+			125	1+
29	100	2+			166	±
30	12	3+			50	0
31	166	2+			>333	0
32	12	1+			100	1+
33	25	2+			50	0
34	67	3+			125	0
35	100	2+			50	0
36	125	3+			167	0
37	67	3+			67	4+
38	40	2+			67	1+
39	67	3+			67	0
40	67	3+			67	3+
41	125	1+			200	0
42	67	1+			67	±
43	100	±			100	0
44	12	2+			50	0
MEAN:	71.5				91.2	

TABLE II. COMPARATIVE INCIDENCE AND LEVELS OF SERUM C-REACTIVE PROTEIN (CRP) AMONG 44 MOTHERS AND NEWBORN BABIES

CRP		SOURCE OF SPECIMEN			
		MATERNAL	NEONATAL		
			CORD	VENOUS	TOTAL
Negative		6 (13.2 per cent)	11	13	24 (54.5 per cent)
Questionable	(±)	2	2	7	9
Positive	1+	11	1	6	7
	2+	12	0	1	1
		(81.8 per cent)			(25 per cent)
	3+	13	0	2	2
	4+	0	0	1	1

less. On checking the history of the mother who had the highest titer (more than 250 units), it was found that she had been in labor en route to the hospital and had delivered her baby on the stretcher.

The CRP titers are shown in Table I, and the respective comparisons in reactivity are summarized in Table II. The majority of the sera from the mothers showed a positive CRP (38 of 44 specimens), varying from a trace to 4 plus. On the other hand, only one half the specimens of neonatal sera showed positive CRP readings (20 of 44 specimens), and most of these were a trace to 1 plus. In this series a higher proportion of positive reactions was found in neonatal venous blood as compared with the cord blood. It is suggested that the difference may be related to the absorption of necrotic tissue from the umbilical stump, in as much as the venous specimens were drawn during the first four days of life.

The electrophoretic protein fractions of the sera of 19 pairs of mothers and infants are shown in Table III, together with the ASLT and CRP performed on the same sera. It can be seen that the serum albumin of each infant, with one exception, is considerably higher than that of its mother. On analysis, the maternal albumin was found to be lower than that of normal adult subjects.[16, 22] In general, the alpha and beta globulin levels of the infant were lower than those of the mothers, there being one exception (Case 10). There were two instances of absent alpha$_1$ among the cord-maternal pairing (Cases 1 and 2). The closest parallel is seen in the gamma fraction, the mother having a slightly higher value than the infant in 13 of the 19 pairs studied. Table IV gives the high-low range for each of these protein fractions, together with the mean values.

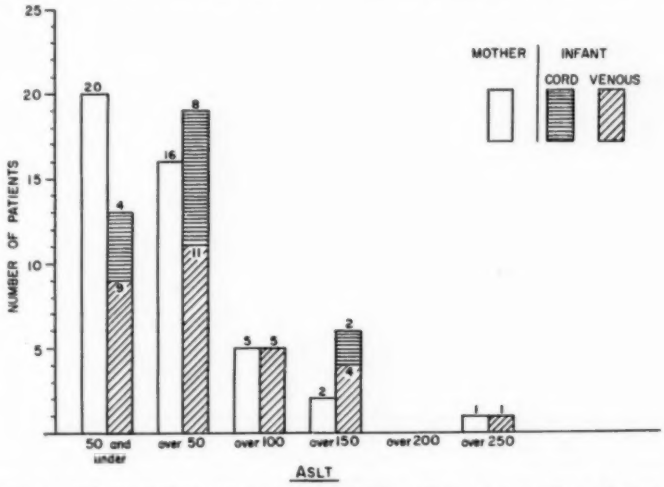

Fig. 2.—Antistreptolysin titers in parturient mothers and newborn infants.

The question may be asked as to whether a high ASLT is reflected in the gamma globulin. Table V gives a comparison between the levels of antistreptolysin and the gamma globulin fractions, from which it can be seen

TABLE III. SERUM PROTEIN FRACTIONS ANALYZED BY ELECTROPHORETIC METHOD, WITH A COMPARISON OF ASLT AND CRP OF 19 MOTHERS AND THEIR NEWBORN INFANTS

CASE NO.		ASLT UNITS/C.C.	CRP MM.	ALBUMIN %	GLOBULIN			
					ALPHA$_1$ %	ALPHA$_2$ %	BETA %	GAMMA %
1	M	12	0	66.2	0	5.5	4.1	24.2
	I	12 C	0	70.9	0	2.7	2.7	23.9
2	M	65	0	49.6	0.8	9.3	16.3	24.1
	I	65 C	0	67.0	0	7.3	7.3	18.4
7	M	12	3+	33.9	7.6	22.9	20.8	15.0
	I	80 C	±	71.1	2.3	7.3	5.4	14.0
8	M	65	3+	55.7	4.5	12.9	13.9	12.9
	I	65 C	1+	73.5	3.1	3.7	8.3	11.5
9	M	135	0	52.0	1.5	9.2	22.2	15.2
	I	65 C	0	74.0	0.8	3.4	4.2	17.6
10	M	50	1+	59.0	3.5	5.8	12.8	18.6
	I	50 C	0	44.9	6.4	14.4	18.2	16.1
11	M	50	1+	40.8	9.4	12.2	16.0	21.6
	I	166 C	0	73.6	2.3	7.0	4.5	12.7
14	M	33	3+	49.1	5.0	14.5	14.7	16.4
	I	33 C	0	73.7	2.1	5.2	4.8	14.2
15	M	50	2+	57.4	5.1	11.6	13.1	12.8
	I	125 V	1+	70.1	2.1	7.3	5.6	14.7
16	M	100	1+	46.9	4.1	9.0	15.8	24.2
	I	100 V	±	66.8	2.0	6.1	6.6	18.5
18	M	50	3+	45.8	5.3	14.8	18.0	16.0
	I	50 V	±	75.8	1.9	5.5	7.2	9.6
19	M	100	2+	41.4	4.2	11.4	22.8	20.4
	I	50 V	±	59.9	2.3	9.0	7.2	21.6
21	M	50	3+	58.2	4.6	14.8	13.0	9.5
	I	100 V	±	66.0	3.0	6.6	11.4	13.0
29	M	100	2+	47.7	3.9	16.5	17.5	14.6
	I	166 V	±	75.5	0.7	6.0	4.5	13.3
30	M	12	4+	39.4	4.0	8.0	27.6	20.4
	I	50 V	0	56.0	3.0	8.2	14.7	18.3
31	M	166	2+	44.2	6.0	16.9	12.9	19.9
	I	333+V	0	70.2	0.8	4.8	9.1	15.1
42	M	67	1+	51.8	4.0	11.8	14.5	17.8
	I	67 V	±	65.5	2.1	6.3	7.3	18.8
43	M	100	±	53.3	5.0	11.2	11.2	19.3
	I	100 V	0	64.3	2.2	7.3	7.9	18.3
44	M	12	2+	48.9	6.6	18.0	17.6	8.9
	I	50 V	0	78.6	1.7	5.4	4.0	10.3

M, Mother; I, infant; C, cord blood; and, V, venous blood.

TABLE IV. RANGE OF VALUES OF PROTEIN FRACTIONS IN PAIRED SERA FROM 19 MOTHERS AND THEIR NEWBORN INFANTS (PER CENT OF TOTAL PROTEIN)

			ALBUMIN	ALPHA$_1$	ALPHA$_2$	BETA	GAMMA
MOTHER	Mean		46.8	4.5	12.4	16.8	17.5
	Range	High	66.2	9.4	22.9	27.6	24.2
		Low	33.9	0	5.5	4.1	8.9
INFANT	Mean		68.3	2.05	6.5	7.4	15.8
	Range	High	78.6	6.4	14.4	18.2	23.9
		Low	44.9	0	2.7	2.7	9.6

that no relationship is suggested between titer levels and gamma readings. Of 13 patients with ASLT of 100 or over, approximately one half had normal levels of gamma globulin.

TABLE V. COMPARISON OF GAMMA GLOBULIN LEVELS AND ASLT

ASLT	GAMMA GLOBULIN: 18%* OR BELOW	GAMMA GLOBULIN: OVER 18%	TOTAL
Under 50	4	3	7
50–	11	7	18
100–	7	6	13
	22	16	38

*Normal value.

From an analysis of our 38 cases (19 pairs) certain correlations could be found between the presence of CRP and the electrophoretic fractions of the globulin. However, these correlations cannot be made with certainty in view of the fact that the CRP and beta globulin, and to a lesser extent the alpha globulin, are commonly elevated in pregnancy. Nevertheless, it is interesting to note that the closest positive correlation between the CRP and serum globulin occurs with the alpha$_2$ component (see Table VI).

TABLE VI. CORRELATION BETWEEN CRP AND ALPHA GLOBULINS

CRP	ALPHA$_{1,2}$ GLOBULINS: 10%* OR BELOW	ALPHA$_{1,2}$ GLOBULINS: OVER 10%	TOTAL
Negative	12	1	13
Questionable	7	1	8
Positive 1+	4	2	6
Positive 2+	0	5	5
Positive 3+	0	5	5
Positive 4+	1	0	1
	24	14	38

*Mean values.

Among 13 patients with a negative CRP, 12 showed normal alpha$_2$ readings. Conversely, among 17 patients with a positive reaction of from 1 to 4 plus, 13 showed alpha$_2$ readings above 10 per cent. This positive correlation conforms with the findings of Perlman and others.[23]

COMMENTS

The evidence for placental transmission of antistreptolysin-O seems clear, as there is a positive correlation between maternal and infant sera. Further evidence may be cited from the work of Lippard and Wheeler[9] who showed, in addition, that there was a diminution in the concentration of antistreptolysin during the infant's first trimester. This is a response typical of passively acquired immune bodies. Moreover, this diminution is known to be coincident with that of the gamma globulin[16, 25] and is of interest in the physiogenesis of gamma globulin.

With regard to the CRP, there seems to be no correlation between the maternal and infant reactions. In this series the infants were noninfected as far as we could determine, hence the negative majority was to be expected. The reverse situation in the cord blood sera is noteworthy, and doubtless sloughing of the umbilical cord was the causative factor in positive reaction. We would agree with the suggestion of Rozansky and Bercovici[13] that there is no transferral of C-reactive protein across the placental membrane.

On reviewing the electrophoretic protein analysis of the paired sera, it will be seen that the normally smaller proportion of alpha and beta globulins in the infant is true also of our series, as is the normally higher proportion of neonatal serum albumin. Moore and others,[14] in their studies of pregnant women at 3 months, 8 months, and at term, found that as pregnancy progressed there was a definite rise in beta globulin, a slight rise in alpha

globulin, but an unchanged level of gamma globulin. Similar to the observations of other authors,[7, 24] our paired sera showed, in general, corresponding levels of gamma (13 of 19 cases); in a few instances the maternal level was higher (5 of 19 pairs).

CONCLUSIONS

From our study of the sera of 44 parturient women and their normal, full-term newborn infants, the following observations are made:

1. The antistreptolysin-O titer of the newborn infant was usually (89 per cent) equal to or greater than that of the mother. The mean titer for the mother was 71.5 and for the infant, 91.2. There appears to be a positive correlation between the titer of related mother and infant, especially when the range is 100 units or below.

2. A positive C-reactive protein titer was found in all except 8 mothers (81.8 per cent positive). All but 3 of the 14 cord blood specimens were negative for this reaction. In contrast, 13 of the 30 infants' venous specimens were positive (43.3 per cent). There would appear to be no transferral of C-reactive protein across the placental membrane.

3. The electrophoretic patterns revealed a decrease in maternal albumin to levels lower than that of the normal adult, and much lower than that of the infant. The relative concentrations of maternal alpha and beta globulins were higher than normal adult values. The gamma globulin fractions of mother and infant were approximately equal.

4. There was no correlation between antistreptolysin-O titer and gamma globulin reading.

5. The high levels of C-reactive protein, and alpha and beta globulins that normally exist in pregnancy may be interrelated. Nevertheless, we conclude that the C-reactive protein is reflected in the $alpha_2$ component.

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LOCAL TISSUE AND BLOOD EOSINOPHILS IN NEWBORN INFANTS

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THE eosinophil is generally thought of as one of the formed elements of the blood involved in immunologic mechanisms. At present little is known about the function of the eosinophil, and a good deal of controversy exists[1] as to its source of origin when found in tissues involved in allergic antigen antibody reactions. Is it transported to such tissue from the bone marrow by way of circulation, or is it formed locally in such tissue as a result of a local immune mechanism? Similarly, is local eosinophilia a specific or nonspecific tissue response? Urbach and Gottlieb[2] state that the outstanding characteristic of allergic intestinal disease is the high eosinophil content of the stool. Vaughn and Black,[3] on the other hand, state that the presence or absence of stool eosinophilia in such cases is of little importance. A. Rosenblum and P. Rosenblum[4] as well as Nance[5] report the presence of numerous eosinophils in the stools of infants having certain types of diarrhea or colic and present clinical evidence favoring food allergy as a basis for such intestinal disorders. In the Roseblums' series of newborn infants, approximately 20 per cent of the cases had stool eosinophils with no gastrointestinal disturbance whatsoever.

The association of local tissue eosinophilia and respiratory allergy is very frequent. Such association is generally considered to be presumptive evidence of respiratory allergy. It is by no means diagnostic, however, as other pathologic states in the respiratory tract may present similar eosinophilia. Samter,[6] after studying eosinophilia in guinea pigs, concluded that eosinophil distribution may be under nonspecific neurohormonal control or may result from a specific antigen antibody mechanism.

The purpose of our study was to evaluate the clinical significance and possibly the mechanism of local tissue eosinophilia in young infants. Our attention was directed to the not infrequent attachment of an allergic etiology to a chronic nasal discharge in a young infant when such discharge contains eosinophils. Similarly, does the presence of eosinophils in the stool of a young infant who has a gastrointestinal disturbance such as colic or diarrhea signify intestinal food allergy? Again, on a few occasions in the past, some vesicular or apparently pustular lesions on the skin of newborn infants, when cultured, were found to be sterile, and when fluid of

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such lesions was examined microscopically it was noted to be almost entirely composed of eosinophils.[11]* We were unable to explain the significance of such skin pathology.

MATERIALS AND METHODS

A group of 129 normal newborn infants, male and female, were included in our study. Nasal smears for cellular study as well as blood examinations for total eosinophil counts were taken on these newborn infants during their stay in the nursery. In many instances rectal smears of stool mucus were obtained by finger insertion into the rectum. Nasal smears were obtained by use of a bulb syringe with a glass tip. The glass tip was inserted into the nostril, mucus was aspirated, transferred to a glass slide, allowed to dry, and then stained with May-Greenwald eosin stain. The eosin stain was applied for 1½ minutes, diluted with distilled water for another 1½ minutes, and finally rinsed with distilled water and allowed to dry. The rectal smears were similarly stained. Nasal and rectal smears were reported as positive for eosinophils when such cells were present in clumps, in strands of mucus, or were numerous in several fields under the high power of the microscope, while "occasional eosinophil" indicated their presence, but in small numbers. Total blood eosinophil counts were made by the usual technique. Two such counts were made on each infant, and the average result was used in order to

Fig. 1.—Nasal smear, eosin stained, from a newborn infant 2 days old. (Arrows point to eosinophil cells.)

*Since then, this clinical observation has been noted and described by Harris and Schick under the name of "erythema neonatorum."

minimize technical error. The diluting fluid used was Pilot's diluting fluid as modified by MacFarlane and Cecil.[7] As advised by the above authors, a time limit of 15 minutes was allowed for the blood and fluid to remain in the pipette to insure lysis and proper staining. In a few instances nasal smears were obtained in the infants immediately after delivery and before silver nitrate was instilled into their eyes. Four specimens of amniotic fluid were also smeared, stained as above, and cytologically examined.

The technique used in obtaining a satisfactory nasal smear is important. The bulb and glass tip used for aspiration should be sterile and dry so that the specimen obtained will not be diluted with water. It is often difficult to aspirate sufficient mucus from the nose of newborn infants. However, if suction is applied several times to one nostril while the other nostril is momentarily occluded, sufficient mucus can be frequently obtained. A cotton swab should not be used as it would absorb the mucus with its cellular content.

Technique of Bone Marrow Aspiration.—After the proper aseptic precautions had been taken, aspiration was done from the flat triangular area at the proximal end of the medial surface of the tibia below the tubercle, by use of standard-gauge 15 sternal needle with the adjustable guard and special locking device for the stylet. Marrow, 0.2 c.c., was aspirated, care being taken to avoid blood contamination in so far as possible, and several smears were made on clean slides. Staining was done by a combination of Wright and Giemsa stains. (The smears were exposed to Wright stain for 2 minutes, then to a buffer solution for 6 minutes, and finally to Giemsa stain for 5 minutes.) A differential count of 300 nucleated cells was then done.

A group of 22 newborn infants were followed periodically in a special outpatient clinic. In this clinic repeat studies of cells in nasal secretions and blood eosinophil counts were done. The general health of these infants with particular emphasis on symptoms of possible allergic etiology was also observed.

Note: Newborn infants in the nursery are not fed milk for the first 24 hours after birth. In the group studied, 63 were later fed breast milk and the remainder (66) a cow's milk formula.

RESULTS

As noted in Table I, 30 per cent of 129 infants examined had positive nasal eosinophilia while 23 per cent of the same group had occasional eosinophils in the nasal smears. Four of these infants had no eosinophils in the nasal smear on the first day of life, but the smears were positive a few days later. There was no apparent relation between presence or absence of nasal eosinophilia and family history of allergy. Eighty-three of the

TABLE I. INCIDENCE OF NASAL EOSINOPHILS IN NEWBORN INFANTS

	POSITIVE	NEGATIVE	OCCASIONAL	TOTAL
Number of infants	40*	60	29	129
Per cent	30	46	23	
Family history† of allergy	1	3	3	7

Positive: eosinophils in clumps, strands, or numerous throughout slide.

Occasional: few scattered eosinophils throughout slide.

*In 4 infants the nasal smears were negative for the first 3 days of life.

†Family history of allergy in the immediate family and includes hay fever, asthma, and urticaria after ingestion of certain foods.

nasal smears were examined in the first 2 days of life and approximately 32 per cent were positive for eosinophils (Table II). When similar examinations were made on another group of infants on the third and fourth days of life, 44 per cent of the nasal smears were positive. This latter group included some infants whose nasal smears were negative in the first 48 hours of life. We were concerned early in our study with the possible effect of prophylactic silver nitrate instillation into the eyes of the newborn infant on nasal eosinophils. No such relationship between these events seemed likely since positive nasal smears were obtained before such silver nitrate instillation.

TABLE II. NASAL EOSINOPHILIA IN THE NEWBORN INFANTS IN FIRST 4 DAYS OF LIFE

	PER CENT POSITIVE	PER CENT NEGATIVE	PER CENT OCCASIONAL	NUMBER OF NASAL SMEARS*
First day	31.5	41.5	27	29
Second day	33	57	10	54
Third day	42	45	13	40
Fourth day	46	54	0	13

*On several infants more than one nasal smear was done.

A gradual increase in blood eosinophils was noted from the second to the fourth day of life in the infants under study (Table III). Burrel[8] also found a gradual increase in blood eosinophils in normal full-term infants. In many instance such increase in blood eosinophils could be correlated with nasal eosinophil increase. This correlation, however, was by no means uniform, especially in the first 4 days of life, as frequently nasal eosinophils were present at a time when blood eosinophils were low, and absent when blood eosinophils were high (Table V). However, when all the infants examined are considered, it is apparent that the blood eosinophil count averaged higher in those infants who had nasal eosinophilia (Table IV, *b* and *d*).

TABLE III. TOTAL BLOOD EOSINOPHIL COUNT IN THE NEWBORN INFANTS

	FIRST DAY	SECOND DAY	THIRD DAY	FOURTH DAY
Number of infants tested	28	33	23	3
Range of eosinophil count per cubic millimeter	111-355	111-355	44-460	244-344
Average eosinophil count per cubic millimeter	126	171	189	307

A gradual increase in blood esinophilia was noted with each day of life from the first to the fourth day, in 87 eosinophil counts.

TABLE IV. BLOOD EOSINOPHILS IN NEWBORN INFANTS

CLASSES OF INFANTS (AVERAGE COUNT)	NUMBER TESTED	BLOOD EOSINOPHIL COUNT PEB CUBIC MILLIMETER
All infants	87	167 (a)
Infants with positive eosinophils in nasal smear	39	203 (b)
Infants with occasional eosinophil in nasal smear	13	173 (c)
Infants with no eosinophils in nasal smear	34	114 (d)
Infants with positive family history of allergy	7	182 (e)
Infants with negative family history of allergy	72	164 (f)

Chi-square analysis of above indicated that (b) and (d) are statistically significant, having P value < 0.01.

No statistical significance could be attached to (a), (c), (e), (f).

The slight increase in blood eosinophils in those infants with family history of allergy is of doubtful significance as the number of such infants studied was too small. Further investigation of this point is necessary for clarification. There was no difference noted in nasal

eosinophilia in the artificially fed infants as contrasted to the breast-fed infants.

The group of infants who were followed periodically in the outpatient clinic for the first 10 months of life presented some interesting data (Table V). There was a gradual increase in blood eosinophils from the first to the seventh week of life. At about 2 to 3 months of life the blood eosinophil count dropped sharply and soon after became stabilized at this lower level until about 10 months of life. Similarly, the nasal eosinophilia frequently —but not constantly—became negative

TABLE V. TOTAL BLOOD EOSINOPHILS IN INFANTS
(Relation to Nasal Eosinophils in Same Infants)

BIRTH*		4-5 WEEKS		6-7 WEEKS		2-3 MONTHS		3-4 MONTHS		4-6 MONTHS		6-8 MONTHS		8-10 MONTHS	
n	355	p	727	n	493	n	289	p	67	n	178	n	155	n	155
p	476	n	155	p	821	n	222	n	133	n	333	n	200	n	89
n	244	p	1576	n	799	n	178	n	333	n	100	n	133	n	155
p	960	p	289	p	396	n	111	n	167	p	67	n	89	n	67
n	165	p	259	n	462	p	444	p	311	n	222	n	411	n	222
p	357	n	400	n	336	n	89	p	311	n	178	p	200	p	333
p	155	n	322	n	342	n	366	n	155	n	89	n	200	p	177
n	200	p	355			n	200	n	111	p	133	p	111	n	335
p	100	n	355			n	644	n	111	n	178	n	155	p	222
n	111	n	133			n	122			p	444	p	78		
p	111	p	333			n	178			n	167	n	111		
p	155					n	178			n	220	n	89		
p	122					n	200								
n	78					n	200								
p	33					n	200								
n	111														
p	56														
Average blood eosinophil per cubic millimeter:															
222		459		521		241		188		192		161		195	

Eighty-seven blood eosinophil counts made at various times from birth to 10 months of age reveal a gradual increase in blood eosinophils until a peak is reached at the seventh week. Subsequently, there is a sharp drop in the eosinophil count. The count then remains fairly constant until the tenth month of age.

*Includes infants from 7 hours to 4 days of age.

p—Nasal secretion was positive for eosinophils.

n—Nasal secretion was negative for eosinophils.

TABLE VI. EOSINOPHILS IN NASAL AND RECTAL SMEARS OF NEWBORN INFANTS FROM BIRTH TILL AGE OF 10 MONTHS

	BIRTH*	3 WEEKS	4-5 WEEKS	6-7 WEEKS	2-3 MONTHS	3-4 MONTHS	4-6 MONTHS	6-8 MONTHS	8-10 MONTHS
Total number† in each age period	129	2	13	3	16	13	16	14	18
Nasal Eosinophils									
Number positive	40	2	4	0	0	2	3	4	3
Per cent positive	30	100	30	0	0	15	19	28	16
Rectal Eosinophils									
Number positive	0	0	1	0	0	3	1	0	0
Per cent positive	0	0	8	0	0	23	6	0	0

From 6 to 12 weeks of age nasal eosinophilia was negative.

*Includes infants from birth to 4 days of age.

†No manifestations of allergy in the entire group studied for 10-month period.

at about 7 weeks of age. It is worthy of note that it is at this latter period that the blood eosinophil count was at its peak. In some instances nasal eosinophilia was present after 3 months of age (Table VI) and in no instance in these cases were there any symptoms which could be associated with allergy. Similarly, although in 5 instances (8.5 per cent) of 60 infants studied, rectal eosinophilia was present, in no case followed for a 10-month period were there any manifestations of allergic origin. Of the 55 infants with no rectal eosinophils, 83 per cent had no family history of allergy (history in the immediate family of hay fever, asthma, or urticaria following ingestion of certain foods).

Results of bone marrow examinations (Tables VII and VIII) are inconclusive. The average number of eosinophils in the marrow of 8 infants who did not have nasal eosinophils was greater than the number of such cells in the marrow of those infants whose nasal secretion was positive for eosinophils. On the other hand, the blood eosinophil content was not appreciably different in these two groups examined.

In our attempt to explain the nasal eosinophilia in these newborn infants, we resorted to examination of some amniotic fluid specimens since the possibility existed that the presence of eosinophils in the nose resulted from transference of such cells from the amniotic fluid. This relation, however, to nasal eosinophilia is not at all clear as in the two instances where the amniotic fluid contained such eosinophils, the nasal smear in the infant was negative for the same.

TABLE VII. BONE MARROW EOSINOPHILIA IN EIGHT INFANTS 2 TO 5 DAYS OF AGE WITH NEGATIVE NASAL SMEARS AND NEGATIVE FAMILY HISTORY OF ALLERGY

INFANT NUMBER	BLOOD EOSINOPHILS PER CUBIC MILLIMETER	BONE MARROW EOSINOPHILS* (PER CENT)
1	355	3.6
2	476	5.5
3	244	4.0
4	960	6.6
5	165	4.0
6	357	5.3
7	300	5.6
8	300	6.9
Average	394	5.18

*Total marrow cells counted = 300.

DISCUSSION

It seems clear from our study that nasal eosinophilia is a frequent finding

TABLE VIII. BONE MARROW EOSINOPHILIA IN EIGHT INFANTS LESS THAN 2 DAYS OF AGE WITH POSITIVE NASAL SMEARS

INFANT NUMBER	NASAL SMEAR FOR EOSINOPHILIA	BLOOD EOSINOPHILS PER CUBIC MILLIMETER	BONE MARROW EOSINOPHILS* (PER CENT)	FAMILY HISTORY OF ALLERGY
1	Numerous	440	1.5	Negative
2	Numerous	198	3.0	Positive
3	Loaded	638	2.5	Negative
4	Numerous	264	2.4	Positive
5	Loaded	2,112	2.5	Negative
6	Loaded, some clumps	264	4.0	Negative
7	Numerous, some clumps	352	2.5	Negative
8	Occasional	855	2.6	Positive
	Average	690	2.67	

Average total leukocyte count in peripheral blood (19 newborn infants) = 19,843 per cubic millimeter.

Range of total leukocyte count in peripheral blood (19 newborn infants) = 15,000-27,290 per cubic millimeter.

*Total marrow cells counted = 300.

in the normal newborn infant. In most instances such eosinophilia persists for 2 to 3 months. Although in some of the infants nasal eosinophilia was associated with blood eosinophilia, in the majority of cases no such correlation existed. Frequently nasal eosinophilia was present in the first day of life, when relative blood eosinopenia was present. An explanation for the presence of this local tissue eosinophilia or for the gradual rise in blood eosinophils from the first to the seventh week of life, followed by a sharp drop to a normal persistent level, cannot be reached at present. Can this finding be related to immature adrenal function and corticoid distribution in the blood and other tissues of the newborn infant?

According to Gardner,[9] the inner zone of the adrenal gland of the newborn infant is markedly hypertrophied. Twenty-four hours after birth this zone begins to involute, and associated with this involution is a precipitous fall in plasma 17-ketosteroids to a low level by the end of the first week of life. Cord plasma corticoid levels are the same as in the adult and supposedly originate from the maternal adrenal corticoids. At the age of 2 days the blood plasma corticoids of the infant are very low and approach a normal level only after the first week or 10 days of life. Since blood corticoid concentration influences the circulating eosinophils, one should expect a gradual fall in blood eosinophils after the first 2 days of life. Our data do not support this (Table III). It is certain that further studies are necessary in an attempt to correlate our findings with corticoid function and distribution in the newborn infant.

As stated previously, controversy exists as to the origin of local tissue eosinophilia. Are such cells formed locally and overflow into the blood, or are they formed in the bone marrow and reach the local tissue by way of circulation following a specific or nonspecific stimulus by the tissue? If the latter theory is correct, it seems that local tissue eosinophilia, as a result of a stimulus, unless a stimulus is constant, should be accompanied by a normal blood eosinophil content or an eosinopenia. On similar grounds, one should expect local tissue eosinophilia to be accompanied by an increase in the marrow eosinophils. Our data do not substantiate this hypothesis. Cooke[10] believes that the discrepancies between the number of eosinophils in the blood and that in the tissues present sufficient reason to assume the existence of two different types of eosinophils. Samter,[6] however, in experiments with guinea pigs suggests that a relationship exists between marrow, blood, and local tissue eosinophils. This author states, however, that his data are not conclusive and that the subject requires more investigation.

The presence of rectal eosinophilia in 5 instances of our group of infants under study is interesting. There was no family history of allergy in these cases and these newborn infants, when followed for a 10-month study period, did not present any gastrointestinal complaints or other symptoms suggestive of allergic etiology. Although present far less frequently than nasal eosinophilia, their presence is suggestive of physiologic rather than pathologic etiology. It is possible that, with improved technique, their presence would be found more frequently than our data indicated. The fact that

they are present in apparently normal newborn infants should caution the physician in attributing such a finding necessarily to gastrointestinal allergy. Their presence in the stool of young infants with intestinal symptoms may signify a normal local tissue response to a specific or nonspecific irritant.

SUMMARY AND CONCLUSION

1. Thirty per cent of 129 normal newborn infants examined had nasal eosinophilia in the first 4 days of life. In many instances such eosinophilia was present on the first day of life.

2. In the majority of the infants, nasal eosinophilia, when present, persisted for 7 to 10 weeks and in some instances for 3 months or longer.

3. Total blood eosinophil counts on these same infants revealed a gradual increase in the number of such cells until these infants reached the age of 7 weeks, at which period there was a sharp drop in the blood eosinophil count. This was followed by a stabilization at a lower level so that at 10 months of age the blood eosinophil count approached that of the normal child or adult.

4. Although frequently nasal eosinophilia was associated with blood eosinophilia, such correlation was not uniform. In many instances nasal eosinophilia was present at a time when relative blood eosinopenia was present. Similarly there was no correlation between bone marrow eosinophil and local tissue eosinophil content.

5. We could not demonstrate any relation between nasal or blood eosinophilia in the group of infants under observation for 10 months and family history or symptoms of allergy.

6. There were 5 instances of rectal eosinophilia. When these cases were observed for a period of 10 months, no clinical evidence of allergy was present.

7. We cannot at present conclude as to the mechanism for the origin of local tissue eosinophilia in the newborn infant.

8. Our data indicate that nasal and to a lesser degree rectal eosinophilia is frequent in the first few months of the infant's life and should be considered as a normal finding unless proved to the contrary.

We are greatly indebted to the members of the hematology department for their valuable aid with bone punctures and analysis of marrow from newborn infants.

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OBJECTIVE EVALUATION OF PATIENTS WITH RHEUMATIC DISEASES

III. Comparison of Serum Glycoprotein, Seromucoid, and C-Reactive Protein Determinations as Methods for the Evaluation of Patients With Rheumatic Fever

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BY PRESENT standards it is considered advisable that patients with rheumatic fever remain at bed rest until subsidence of systemic inflammatory activity. Gross clinical signs of the disease ordinarily subside rapidly, rendering the appraisal of lesser degrees of rheumatic fever activity difficult. Acute phase protein reactant tests appear to express quantitative relationship to systemic inflammatory activity and would thus be expected to be of value in assessing rheumatic fever activity.

Serum glycoprotein, seromucoid, and C-reactive protein determinations have been successfully utilized as objective tests for assessing the activity of the rheumatoid process in patients with rheumatoid arthritis.[1, 2] Studies by Kelley have indicated that the serum glycoproteins[3, 4] and seromucoid[5, 6] are elevated in active rheumatic fever. Shetlar and associates[7] presented data concerning the changes of serum glycoprotein, serum hexosamine, sedimentation rate, and heat coagulation values during the course of treatment of several adult patients with recurrent rheumatic fever. The choice of such laboratory aids is dependent upon several factors, including sensitivity, accuracy, speed of change, and ease of performance in the clinical laboratory. The present study has been concerned with the comparison of laboratory tests used in the evaluation of systemic inflammatory activity as aids for the estimation of the severity and duration of activity of rheumatic fever.

MATERIALS AND METHODS

Serum glycoprotein (hexose polysaccharide) was determined by the tryptophan method of Shetlar and associates.[8] Seromucoid was isolated by the method of Weimer and Moshin[9] and quantitated by the tryptophan reaction. Serum protein was determined by the biuret method of Weichselbaum.[10] C-reactive protein determinations were performed by the method of Anderson and McCarty[11] employing commercial C-reactive protein antiserum,* and antistreptolysin O determinations were carried out by the method of Ranty and Randall.[12]

Patients were selected for study from the pediatric wards of Crippled

From the departments of Biochemistry, Pharmacology, Pediatrics, and Medicine, University of Oklahoma School of Medicine, and the Research Laboratory, Veterans Administration Hospital.

*Schieffelin & Company.

Children's Hospital. They were classified by clinical means as "active" or "inactive" at the time that blood samples were drawn. Data presented in the "inactive category" represent patients who were assumed to have amply recovered from rheumatic fever.

titer are summarized in Table I. In contrast to the glycoprotein and seromucoid data, the CRP was positive in only 1 of 15 cases rated inactive clinically. On the other hand, 3 of 15 active cases had negative C-reactive proteins. Sixteen of 18 active cases had

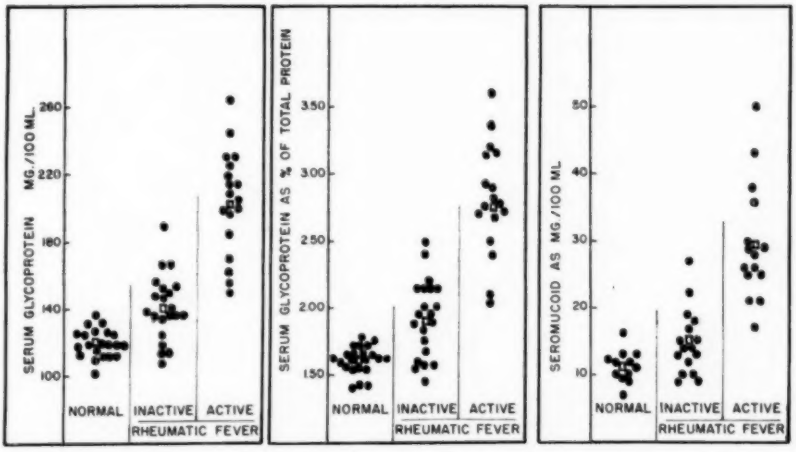

Fig. 1.—Serum glycoprotein and seromucoid in normal subjects and in patients with active and inactive rheumatic fever. Serum glycoproteins are expressed on the left as milligrams of bound hexose per 100 ml. of serum and in the center as a percentage of the total serum protein, i.e., grams of bound hexose per 100 grams of protein. Squares indicate the average for each group.

RESULTS

Serum glycoprotein and seromucoid concentrations of patients with active and inactive rheumatic fever are presented in Fig. 1. All of the patients with active disease exhibited elevated glycoprotein levels, whether expressed in terms of milligrams of bound hexose per 100 ml. of serum or as a percentage of the total serum protein. Many of the patients who were considered inactive clinically also had elevated serum glycoprotein levels. In general, the seromucoid levels were similarly elevated in the active stage and often still elevated in the inactive phase.

The data for C-reactive protein (CRP) and antistreptolysin O (ASO)

ASO titers in excess of 1:50, while 15 of 16 inactive cases had ASO titers in excess of this figure. The erythrocyte sedimentation rate (ESR) was elevated in 14 of 16 cases of active rheumatic fever (one of the active cases with a normal sedimentation rate later exhibited an elevated rate) and in 13 of 15 of inactive cases. However, most of the active cases which became inactive under study exhibited decreased although still elevated sedimentation rates.

Two typical cases which were studied serially are presented in Figs. 2 and 3. The times required for the tests to reach normal levels in several cases are summarized in Table II.

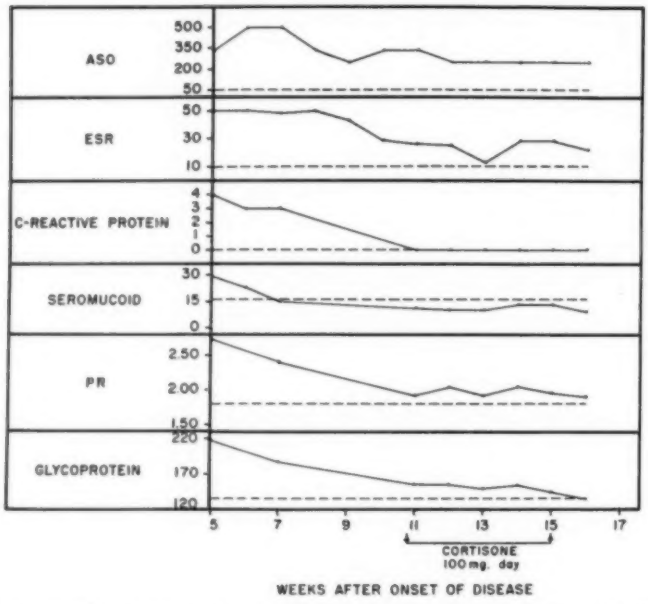

Fig. 2.—Serial studies of an 11-year-old girl with rheumatic fever. Patient became clinically asymptomatic at the fifteenth week. Broken lines indicate the highest normal level for the respective test.

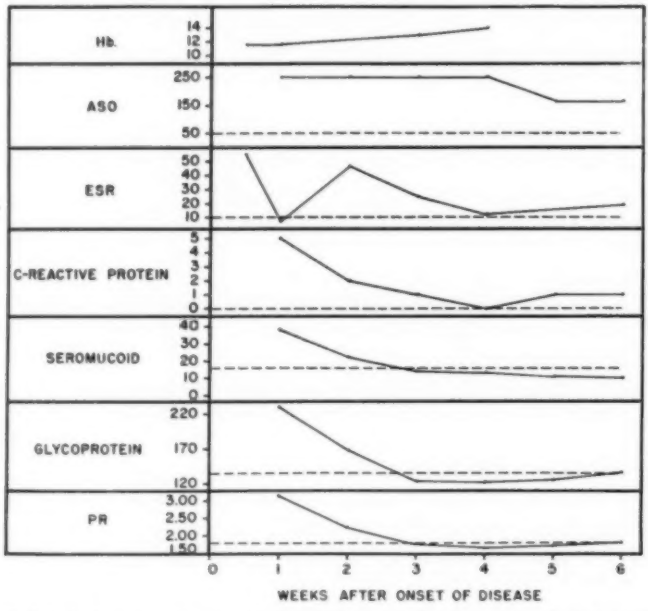

Fig. 3.—Serial studies of a 9-year-old girl with rheumatic fever. Patient became asymptomatic at the second week. Broken lines indicate highest normal level for the respective test.

TABLE I. SUMMARY OF LABORATORY TESTS USED FOR EVALUATION OF RHEUMATIC FEVER PATIENTS

DETERMINATION	ACTIVITY	NUMBER OF CASES	NUMBER ELEVATED	AVERAGE*	RANGE
Glycoprotein (mg./100 ml.)	Active	18	18	205 ± 7.3	151-244
	Inactive	21	9	104 ± 4.4	106-191
	Normal	21	0	120 ± 1.8	100-137
Glycoprotein (PR)	Active	18	18	2.78 ± .10	2.03-3.36
	Inactive	21	15	1.91 ± .06	1.56-2.48
	Normal	21	0	1.63 ± .02	1.41-1.77
Seromucoid	Active	15	15	30 ± 2.3	17-50
	Inactive	16	4	15 ± 1.2	9-27
	Normal	12	0	11 ± 0.7	9-16
C-reactive protein	Active	15	12	2.5	0-5
	Inactive	15	1	0	0-1
	Normal	24	0	0	0
Antistreptolysin O	Active	17	15	508	12-1250
	Inactive	18	16	289	100-833
	Normal	24	0	---	0-50
Erythrocyte sedimentation rate	Active	16	14	42	4-58
	Inactive	18	13	25	8-44
	Normal	--	--	---	0-10

*Figures following ± sign are standard errors of the mean of each group.

TABLE II. DAYS AFTER BEGINNING OF THERAPY REQUIRED FOR FIRST APPEARANCE OF NORMAL VALUES

PATIENT	AGE	NUMBER OF DAYS FOLLOWED	CLINICAL	GLYCOPROTEIN		SEROMUCOID	C-REACTIVE PROTEIN
				MG./100	PR		
O. B.	6	21	7	SE*	SE	SE	7
M. C.	9	35	7	14	14	14	21
B. F.	8	35	21	SE	SE	28	14
G. F.	8	35	14	SE	SE	28	21
C. H.	11	42	14	42	42	21	7
G. J.	11	77	7	77	42	14	14
D. M.	6	48	7	SE	49	25	25
L. R.	13	119	66	112	90	90	21
B. S.	10	19	7	19	19	14	14

*SE indicates that test remained slightly elevated during course of the study.

ASO values are least responsive to changes in activity followed by erythrocyte sedimentation rate and serum glycoprotein, in the order of least responsiveness. The C-reactive protein level appeared to show several changes in inflammatory activity most rapidly and the seromucoid level was next most rapid. In general, patients were considered clinically asymptomatic before any of the tests became normal.

DISCUSSION

The ESR, a traditional index of inflammatory activity, while elevated in most cases of active rheumatic fever, shows an erratic and prolonged return to normal in many patients with rheumatic fever. Although this test is easily performed, it would appear to reflect rather poorly the quantitative aspects of rheumatic fever activity. The data in Table I indicate that the ESR does not provide a sharp boundary between severe active and inactive rheumatic fever.

C-reactive protein determinations are easily performed with the aid of commercially available C-reactive protein antiserum. This precipitin test

is elevated in a majority of patients with acute rheumatic fever but probably returns to normal before complete subsidence of inflammatory activity. It would thus appear to show good correlation to the severe inflammation characteristic of the early phase of rheumatic fever but probably is not sufficiently sensitive to serve as an index of lesser degrees of activity. Furthermore, certain care must be taken with this test. Many of the same samples reported in Table I were subjected to C-reactive protein determinations in one of the University Hospital routine clinical laboratories. This laboratory reported only seven positive CRP values in the series of 15 active cases.

On the evidence obtained in the present study seromucoid concentrations would appear to express closely the degree of inflammatory activity in rheumatic fever. This serum component shows a smooth and consistent decline with decreasing inflammatory activity in rheumatic fever and usually provides a clear separation between active and inactive phases of the disease. It has the disadvantage, as does the glycoprotein determination, of requiring relatively exacting technique in its performance.

Serum glycoprotein was found to be elevated in all patients with acute rheumatic fever and showed a smooth decline with subsidence of activity; however, its return to normal levels occurred somewhat later than seromucoid. The reason for this difference is not easily apparent. The serum glycoproteins probably contain components which are affected by pathological processes other than inflammation or components which change more slowly after the subsidence of inflammation than does the seromucoid. The answer to this question must await more precise analysis of the individual glycoprotein moieties.

The PR ratio, which has proved in this laboratory to be a most dependable index of inflammatory activity in patients with rheumatoid arthritis, shows no clear superiority over glycoprotein determinations alone in the series of children with rheumatic fever in this study. This is apparently due to the fact that alterations in serum protein levels are less striking in children with rheumatic fever.

Antistreptolysin titers, while of considerable value for the diagnosis of rheumatic fever, show no clear relationship to current inflammatory activity of the disease.

The problem of assigning an end point to rheumatic fever activity by laboratory aids has not been clearly solved. The complete battery of tests that has been described is obviously not practical for the routine evaluation of rheumatic fever. These studies, however, appear to indicate that either the seromucoid or serum glycoprotein levels show considerable promise in this regard. However, further studies are indicated to determine the level of these components where hospitalization and therapy may safely be terminated.

SUMMARY AND CONCLUSION

Serum glycoprotein, seromucoid, and C-reactive protein determinations were compared with erythrocyte sedimentation rates and antistreptolysin O determinations as means of evaluating rheumatic fever patients. In general, patients were rated clinically inactive before any of the laboratory

tests reached normal levels. As activity subsided, C-reactive protein fell most rapidly, followed by seromucoid, then by serum glycoprotein, and then by sedimentation rates and antistreptolysin titer.

We gratefully acknowledge the aid of Mrs. Charlsae Branam in determining the erythrocyte sedimentation rates and antistreptolysin titers.

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ACELLULAR BACTERIAL ANTIGEN COMPLEX (HOFFMANN) IN THE TREATMENT OF CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS AND INFECTIOUS ASTHMA

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INTRODUCTION

THE concept that susceptibility to frequent respiratory infections is apt to fall gradually after the age of 5 years as a child develops his own protective mechanism is usually not applicable to allergic children. This particular group of children often grows into greater trouble with advancing age and indeed some never outgrow susceptibility unless immunized repeatedly with effective bacterial antigens. The groundwork of asthma, acute or chronic, is laid in many cases in infancy and childhood.[1, 2]

The advent of potent antibiotics has failed to solve many of the problems arising from respiratory infections in children. Of course, some of the bacteria and most of the viruses and fungi have never been affected by antibiotics. The noncritical use of antibiotics in mild infections is very likely to interfere with the production of immune bodies.[3] Infants and children with repeated upper respiratory infections continue to lack resistance to bacterial invasion, and many of them develop the serious complication of infectious asthma.

The repeated use of antibiotics in the treatment of these cases is only a palliative measure and may result in severe allergic reactions to the drugs themselves.[4-6] Even more important, they may cause the development of resistant strains of bacteria,[7-9] as well as the overgrowth of a normally depressed bacterial flora which frequently is equally detrimental to the patient.[10] Their use therefore should be reduced to a minimum in the treatment of chronic, recurrent respiratory infections and infectious asthma.

Dowling, Lepper, and Jackson[7] have clearly stated the need for measures designed to improve the hosts' defenses. They do not consider that acute infections represent the main problem. They surmise that the plagues of the future will be the chronic infections of the respiratory tract, the urinary tract, the intestinal tract, and the skin, and have come to the conclusion that antibiotic-resistant microorganisms will remain an important problem in the control of infections and will probably become a problem of increasing gravity.

The treatment of choice in the management of chronic respiratory infections and infectious asthma is inoculations of properly prepared bacterial antigens which are potent

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enough and complete enough to immunize the patient and to desensitize as well.

In the past many children have been treated with vaccines for the prevention and management of respiratory infections. Allergists, and pediatricians in particular, have found that respiratory vaccines have their place in the treatment of infectious asthma and that in selected cases not only do they reduce the sensitivity to secondary invaders but also in some cases actually reduce the incidence of colds. In spite of their frequent and accepted use as an adjunct in the treatment of asthma most clinicians are concerned with the large percentage of failures and the numerous patients in whom vaccines, autogenous or stock, aggravate existing asthma or initiate attacks even when highly diluted.[11, 12]

There has been some indication of the usefulness of bacterial filtrates.[13, 14] These filtrates while containing some valuable antigenic substances also contain peptones, meat extracts, sugar, and frequently animal sera which in themselves are sensitizing in nature.

The unsatisfactory results obtained with vaccine therapy and other therapeutic measures prompted the author to investigate a new type of acellular bacterial antigen. Such antigens prepared according to the method of Hoffmann[15] have been found to be singularly effective in the treatment of recurrent respiratory infections and infectious asthma,[16, 18] and in the treatment of chronic brucellosis.[19, 21]

MATERIALS

Acellular bacterial antigen complex preparations made according to the method of Hoffmann.[15*]

As the name implies, the antigens produced by this method are complex in nature. They contain the soluble specific substances of the bacterial cell such as pneumococcal polysaccharides, the "M" substance in group A hemolytic streptococci, and/or Boivin antigen in gram-negative bacteria which are generally accepted as indispensable for protective immunization and the enzymes and toxins of the respective organisms. These, namely scarlet-fever toxin, hemolysin, leukocidin, dermonecrotic toxin, coagulase, and hyaluronidase, are formidable antigens useful for desensitization and are absent in ordinary vaccines.

The antigens prepared according to the Hoffmann method differ from vaccines by being acellular, water-clear solutions of the previously mentioned antigenic components. The process used eliminates the bacterial cell and with it 90 to 95 per cent of the nonessential, sensitizing bulk present in vaccines. The process of producing these acellular antigens also eliminates up to 94 per cent of the nitrogenous substances which are present in the culture medium.

Three varieties of acellular bacterial antigen complex preparations were used in this study. For brevity these antigens are hereafter referred to as B.A.C.

*The acellular bacterial antigen complex preparations were made by the Hoffmann Laboratory, 666 Broadway, Paterson 4, New Jersey.

1. *Autogenous B.A.C.* prepared from organisms isolated from various foci of infection and exudates in the respective patients, such as nose, throat, sputum, and in one instance from cultures isolated from tonsils after tonsillectomy.

The organisms isolated in the order of frequency, were as follows: *Micrococcus pyogenes* var. *aureus,* coagulase positive 11; pneumococci 9; hemolytic streptococci 6; *Streptococcus viridans* 4; *Neisseria catarrhalis* 3; nonhemolytic streptococci 2; *Hemophilus influenzae* 1; and coliform bacillus 1.

2. *Respiratory B.A.C.* prepared from freshly isolated virulent cultures of Streptococci (hemolytic, nonhemolytic, and viridans); pneumococci, *Micrococcus pyogenes* var. *aureus* and *albus, B. coli, Neisseria catarrhalis,* and *H. influenzae*—all obtained from active infections and stock strains of hemolytic streptococci, group A, types 2, 3, and 12 and nonhemolytic streptococci.
3. *Pooled Stock B.A.C.* No. 1 prepared from typed strains of pneumococci, types I, II, V, VII, and XIV; hemolytic streptococci, group A, types 3, 10, 12, and Granger (arthritic strain); *Micrococcus pyogenes* var. *aureus* and *albus; Streptococcus viridans,* strains R 1551, R 1822, and R 353; *Neisseria catarrhalis, Escherichia coli,* and *H. influenzae,* types A and B.

The autogenous B.A.C. were prepared in concentrations of 30 to 70 meg. of nitrogen per c.c. and the respiratory B.A.C. and pooled stock B.A.C. No. 1 were standardized to contain 120 meg. of nitrogen per c.c.

SELECTION OF PATIENTS

Twenty-five children, 15 males and 10 females, ranging in age from 2½ to 14 years were selected for treatment because of frequently recurring respiratory infections. Seventeen of the children had developed bronchial asthma. The conditions existing in these children have been graded as "severe" in eleven instances, "moderately severe" in ten instances, and "mild" in four. Thirteen of the children had previously been treated with commercially obtainable cellular vaccines or autogenous vaccines for periods ranging from one to seven years.

Thirteen of the children have been under the pediatric care of the author for from five to thirteen years, seven for from two to four years, and five from birth to one year. The duration of illness ranged from one and one half to eleven years.

All of the children had previously been treated symptomatically with sulfonamides, antibiotics, antihistaminic drugs, and other available medication, including vaccine therapy in thirteen instances.

Nineteen of the twenty-five children gave a positive family history of allergy. The pathology present in six of the children was believed to be due to infection alone. In nineteen cases infection was complicated by nonbacterial allergies such as pollens, grasses, food, etc., and these patients were under treatment with inhalant extracts and with elimination diets. All of them however suffered from frequent colds, and in the asthmatic group each new infection aggravated or initiated attacks.

In the following tables the children have been divided into two groups, namely "infectious asthma" and "frequent respiratory infections."

TABLE I. HISTORY AND DIAGNOSIS OF PATIENTS SELECTED FOR TREATMENT WITH ACELLULAR BACTERIAL ANTIGEN COMPLEX PREPARATIONS

			DIAGNOSIS				
CASE	SEX	AGE (YR.)	FAMILY HISTORY OF ALLERGY	INFECTIOUS, OR INFECTIOUS PLUS OTHER ALLERGIES	GRADE	DURATION ILLNESS (YR.)	AGE FIRST SEEN
			Infectious Asthma				
1	F	6	Positive	Infectious	Severe	1½	3½ yr.
2	F	2½	Positive	Infectious	Mod. severe	1½	2 yr.
3	M	14	Positive	Infectious +	Severe	11	1 yr.
4	F	9	Positive	Infectious +	Severe	5	5½ yr.
5	M	11	Positive	Infectious +	Mod. severe	5	4 yr.
6	M	4	Positive	Infectious +	Severe	2	2 yr.
7	F	13	Positive	Infectious +	Severe	9	9 yr.
8	F	11	Positive	Infectious +	Severe	10	10 yr.
9	M	5	Negative	Infectious +	Mod. severe	3	1 mo.
10	M	10	Positive	Infectious +	Mild	5	2 yr.
11	F	10	Positive	Infectious +	Mild	2	4 yr.
12	M	12	Negative	Infectious	Mild	1	8 yr.
13	F	9	Positive	Infectious	Mild	1	5 mo.
14	F	6	Positive	Infectious +	Severe	3	3 yr.
15	M	4	Positive	Infectious +	Mod. severe	1	4 yr.
16	M	9	Positive	Infectious +	Severe	4	3 yr.
17	M	12	Positive	Infectious +	Mod. severe	10	6 yr.
			Frequent Respiratory Infections				
18	M	8	Positive	Infectious +	Severe	7	Birth
19	M	11	Positive	Infectious +	Severe	10½	6 yr.
20	M	11	Negative	Infectious +	Severe	10½	Birth
21	M	4	Positive	Infectious +	Mod. severe	3½	5 mo.
22	F	7	Negative	Infectious +	Mod. severe	6	1 yr.
23	F	12	Negative	Infectious	Mod. severe	10	10 yr.
24	M	9	Positive	Infectious +	Mod. severe	8½	Birth
25	M	6	Negative	Infectious	Mod. severe	3	5 yr.

Table I shows the history and diagnosis of the patients selected for treatment.

METHOD OF TREATMENT

Thirteen children were treated with autogenous B.A.C.; six cases with respiratory B.A.C. and six with pooled stock B.A.C. No. 1.

Inoculations were given by the intradermal route and routinely every four to five days for four weeks; once weekly for four weeks; biweekly and then monthly or booster injections were given when indicated for prophylaxis. The interval between injections and the length of treatment were adapted to the individual case.

Initial injection consisted of 0.01 c.c. and the clinical response of the patient noted and recorded before next injection. In most instances skin test reactions were observed and recorded as immediate (8 to 15 minutes) or delayed (24 hours). Any aggravation of asthma or respiratory infection, however slight, was an indication for dilution of the particular B.A.C. used.

After skin testing, treatment was commenced with a dosage of 0.02 c.c. intradermally (sufficient to produce a wheal of approximately 2 mm. in diameter). This dosage was maintained throughout treatment.

In those cases treated with autogenous B.A.C. the patient was skin tested with one autogenous B.A.C. at a visit. After completion of skin testing with the respective autogenous

B.A.C., two, and in some cases three, autogenous B.A.C. were used at the same visit, separate inoculations being made at skin sites approximately one and one half inches apart. Later in treatment these autogenous B.A.C. were usually combined and injected as one dose of 0.02 c.c. intradermally.

SKIN TEST REACTIONS

B.A.C. preparations elicit mainly skin test reactions of the immediate wheal type. Of the recorded skin test reactions, twenty-one were immediate, eight were negative, and only two showed delayed reactions.

Table II shows the type of B.A.C. preparation used for treatment, the organisms isolated in those cases for whom autogenous B.A.C. were prepared, and the skin test reactions.

RESULTS OF TREATMENT

Results of treatment with selected B.A.C. preparations and comparison with previous cellular vaccine therapy are summarized in Table III.

Results were recorded as "excellent" when acute respiratory infections became rare, short in duration, and unaccompanied by asthma. A recording of "very good" indicates a definite decrease in frequency and severity of colds and a marked decrease in the incidence and severity of accompanying asthma. "Good" indicates a significant but moderate decrease in frequency and severity of colds and accompanying asthma. The author has been conservative in labeling these results as "good" since all of the parents of the children in this group are impressed with the results obtained.

Of the seventeen cases of asthma the results were excellent in six cases, very good in six, good in three, good but inconclusive in one because tonsillectomy was performed from which specimen this patient's autogenous B.A.C. were prepared, and poor in one case.

Of the eight cases treated for frequent upper respiratory infections without accompanying asthma, the results were excellent in two cases, very good in five, and good in one.

Results in thirteen cases were dramatic. After one, two, or three injections of B.A.C. wheezing and dyspnea ceased and improvement in chronic cough or chronic nasal discharge was noted. The rapidity of response in all patients (except one failure) was in striking contrast to results obtained with standard cellular vaccines, stock or autogenous.

Thirteen of the twenty-five children had previously been treated with the standard type of cellular vaccines, either stock or autogenous and therefore constitute their own control group. Results of previous vaccine treatment had been poor in eleven cases. Two cases showed fair improvement for a time and then their symptoms returned with greater severity. In four of the children previously treated with vaccines, symptoms were aggravated by treatment even when these standard vaccines were injected in diluted form. Treatment of these thirteen children with B.A.C. resulted in excellent relief in five cases, very good relief in six, good improvement in one, and no improvement in one.

In a few (four) particularly hypersensitive cases initial skin testing with full strength B.A.C. elicited an aggravation of symptoms, but in all of these cases dilution of the B.A.C.

TABLE II. TYPE OF B.A.C. USED FOR TREATMENT AND INCIDENCE OF IMMEDIATE WHEAL TYPE SKIN REACTIONS

CASE	TYPE OF B.A.C. USED	SKIN REACTION	
		IMMEDIATE	DELAYED
	Infectious Asthma		
1	Autogenous		
	No. 1 pneumococci	1+	
	No. 2 *M. pyogenes* var. *aureus*	1+	
	No. 3 *B. coli*	0	
	No. 4 *N. catarrhalis*	0	
2	Autogenous		
	No. 1 pneumococci and hemolytic streptococci	Not recorded	
	No. 2 *H. influenzae*	Not recorded	
3	Autogenous		
	No. 1 *Streptococcus viridans*	1+	
	No. 2 *M. pyogenes* var. *aureus*	2+	
4	Autogenous		
	No. 1 pneumococci	2+	
	No. 2 *Streptococcus viridans*	2+	
5	Autogenous		
	No. 1 pneumococci	1+	
	No. 2 *M. pyogenes* var. *aureus* and *N. catarrhalis*	0	
6	Autogenous		
	No. 1 hemolytic streptococci and *M. pyogenes* var. *aureus*	1+	
	No. 2 pneumococci	2+	
7	Autogenous		
	No. 1 nonhemolytic streptococci	0	
	No. 2 *M. pyogenes* var. *aureus*	0	
8	Autogenous		
	No. 1 *M. pyogenes* var. *aureus*	Not recorded	
	No. 2 hemolytic streptococci	Not recorded	
9	Autogenous		
	No. 1 pneumococci and hemolytic streptococci	1+	
	No. 2 *M. pyogenes* var. *aureus*	1+	
10	Autogenous		
	No. 1 pneumococci and nonhemolytic streptococci	0	
	No. 2 *M. pyogenes* var. *aureus*	0	
11	Respiratory B.A.C.	Not recorded	
12	Respiratory B.A.C.	2+	
13	Pooled stock B.A.C. No. 1	Not recorded	
14	Respiratory B.A.C.	Not recorded	
15	Respiratory B.A.C.	Not recorded	
16	Pooled stock B.A.C. No. 1	1+	
17	Pooled stock B.A.C. No. 1	1+	2+
	Frequent Respiratory Infections		
18	Autogenous		
	No. 1 *Streptococcus viridans*	±	
	No. 2 hemolytic streptococci	1+	
19	Autogenous		
	No. 1 *M. pyogenes* var. *aureus*	1+	
	No. 2 *Streptococcus viridans*	1+	
	No. 3 pneumococci	1+	
20	Autogenous		
	No. 1 pneumococci	1+	
	No. 2 hemolytic streptococci	1+	
	No. 3 *M. pyogenes* var. *aureus*	1+	
21	Pooled stock B.A.C. No. 1	Not recorded	
22	Pooled stock B.A.C. No. 1	0	2+
23	Pooled stock B.A.C. No. 1	Not recorded	
24	Respiratory B.A.C.	Not recorded	
25	Respiratory B.A.C.	Not recorded	

TABLE III. RESULTS OF TREATMENT WITH ACELLULAR BACTERIAL ANTIGEN COMPLEX (B.A.C.) AND COMPARISON WITH PREVIOUS CELLULAR VACCINE THERAPY

DIAGNOSIS			TREATMENT WITH ACELLULAR BACTERIAL ANTIGEN COMPLEX (B.A.C.) AND RESULTS					
CASE	INFECTIOUS, OR INFECTIOUS PLUS OTHER ALLERGIES	DURATION OF ILLNESS (YEARS)	PREVIOUS CELLULAR VACCINE TREATMENT RESULTS	AGE B.A.C. STARTED (YEARS)	TYPE OF B.A.C. USED	FIRST RELIEF NOTED	DURATION TREATMENT (MONTHS)	RESULTS
	Infectious Asthma							
1	Infectious	1½		5	Autogenous	First injec.	11	Very good
2	Infectious	1½		2½	Autogenous	First injec.	17	Very good
3	Infectious +	11	Fair, temporarily	14	Autogenous	First to third injec.	16	Excellent
4	Infectious +	5	Poor	9	Autogenous		4½	Failure
5	Infectious +	5		11	Autogenous	First to second injec.	18	Excellent
6	Infectious +	2		4	Autogenous	1 month	17	Very good
7	Infectious +	9	Poor	13	Autogenous	First inject.	17	Excellent
8	Infectious +	10		11	Autogenous	First to third injec.	20	Good
9	Infectious +	3		3	Autogenous		15	Good, inconclusive*
10	Infectious +	5	Poor	10	Autogenous	Third injec.	15	Excellent
11	Infectious +	2	Poor	10	Respiratory B.A.C.	First injec.	19	Very good
12	Infectious	1	Poor	12	Respiratory B.A.C.	First to third injec.	13	Excellent
13	Infectious	1		9	Pooled stock B.A.C. No. 1	Second injec.	11	Excellent
14	Infectious +	3	Poor	6	Respiratory B.A.C.		14	Very good
15	Infectious +	1	Poor	4	Respiratory B.A.C.		12	Very good
16	Infectious +	4	Poor	9	Pooled stock B.A.C. No. 1		12	Very good
17	Infectious +	10	Poor	12	Pooled stock B.A.C. No. 1		12	Good
	Frequent Respiratory Infections							
18	Infectious +	7		8	Autogenous	Second injec.	20	Very good
19	Infectious +	10½	Poor	11	Autogenous	First to third injec.	20	Excellent
20	Infectious +	10½		11	Autogenous		15	Very good
21	Infectious +	3½		4	Pooled stock B.A.C. No. 1	1 month	12	Good
22	Infectious +	6		7	Pooled stock B.A.C. No. 1		11	Good
23	Infectious	10	Good, temporarily	12	Pooled stock B.A.C. No. 1		11	Very good
24	Infectious +	8½	Poor	9	Respiratory B.A.C.		20	Very good
25	Infectious	3		6	Respiratory B.A.C.	First injec.	14	Excellent

*Case 9. Result good but inconclusive. T & A done Feb. 6, 1956, and autogenous B.A.C. prepared from operative specimens.

(1:5, 1:10, or 1:25) permitted treatment to be resumed without side effects and after treatment with diluted B.A.C. for about one month, these patients were treated with full strength B.A.C.

It must be made clear that the results obtained with B.A.C. in the seventeen cases of bronchial asthma have been in relation to respiratory infections and their influence on asthma. Those children whose asthma was affected by ingestion of specific foods or by contact with inhalants continued to have attacks if these factors were allowed to operate. This is illustrated in the report on Case 7 following, when on two separate occasions after eating tuna fish the patient had mild attacks of asthma.

The use of B.A.C. is advocated as an adjunct in the treatment of infectious asthma and not as a substitute for the type of allergy treatment that results from the taking of a careful history, making a complete physical examination, and doing allergy tests where indicated.

CASE REPORTS

CASE 1.—This 6-year-old girl had her first attack of asthma in March, 1954, and attacks followed in December, 1954, March and December, 1955, and early in May, 1956. The last three of these were severe, requiring Adrenalin and/or Meticorten for their control. All attacks were associated with respiratory infections.

In May, 1956, cultures of nose and throat were positive for pneumococci, *Micrococcus pyogenes* var. *aureus* (hemolytic and coagulase positive), *B. Coli* and *Neisseria catarrhalis*. Autogenous B.A.C.'s were prepared from the individual cultures. On intradermal testing the first two gave positive immediate reactions. These two autogenous B.A.C.'s were combined and treatment was started with this combined autogenous B.A.C. on June 5, 1956, with doses of 0.02 c.c. given intradermally once a week for five weeks, then every three to four weeks until the spring of 1957.

Since June, 1956, she has had many mild and four more severe colds. Three of the latter were associated with mild wheezing and were easily controlled by oral therapy. She has required no antibiotics since autogenous B.A.C. treatment was instituted. The mother states that this past winter has been the first one that this child has been well enough to go out and participate in winter sports.

CASE 7.—This 14-year-old girl began to have asthma in 1946 at the age of 3 years. Colds were usually followed by acute asthmatic bronchitis which took from one to three weeks to clear up. In 1947 her tonsils and adenoids were removed and her asthma increased in severity thereafter. Attacks of asthma were more severe in the fall, but colds and asthmatic bronchitis were frequent throughout the winter and spring. Skin tests were positive to ragweed, dust, and numerous foods. Treatment with ragweed, dust, and commercial catarrhal vaccines from 1946 to 1951 and from 1953 to 1955 resulted in very little change in her asthma. In 1954 and 1955, respiratory infections were aggravated or often initiated by the administration of catarrhal vaccine. When the vaccine was diluted sufficiently to avoid such reactions there was no apparent beneficial effect.

Because of her lack of improvement, cultures were taken from nose and throat and sputum. A nonhemolytic streptococcus was obtained from the cultures taken from the sputum and throat, and *Micrococcus pyogenes* var. *aureus*, hemolytic and coagulase positive, was obtained from the nose. Two autogenous B.A.C.'s were prepared, and on Dec. 5, 1955, treatment was begun. The inoculations were

given intradermally at skin sites approximately one and one half inches apart, dosage of each autogenous B.A.C. 0.02 c.c. Injections were given at four- to five-day intervals for the first three weeks and then continued once every two to four weeks.

Since treatment was begun with the two autogenous B.A.C.'s this child has had only mild upper respiratory infections which cleared spontaneously. Two of these were accompanied by asthma of mild severity. She has required no antibiotics since the onset of B.A.C. treatment.

In March and again in July, 1956, after eating tuna fish she had a mild attack of asthma. This patient's result with the present treatment has been excellent, and the past two winters have been her best ever. She has been able to enjoy skating without wheezing for the first time in her life.

CASE 11.—This 10-year-old child began to have asthma when she was 7 years of age. Her attacks of asthma were preceded by colds and became increasingly more severe. As an infant she had eczema and hay fever and gave positive skin tests to house dust, feathers, and ragweed. Treatment with these allergens and with Hapamine was instituted, but her asthma remained essentially the same.

On Oct. 17, 1955, she was placed on respiratory B.A.C. This antigen was given intradermally in a dose of 0.02 c.c., and marked improvement indicated by complete freedom from wheezing resulted with the first inoculation. On Dec. 4, 1955, she had a mild pharyngitis which was not followed by asthma. Treatment with respiratory B.A.C. was continued at four- to five-day intervals for several weeks and then at two- to four-week intervals.

This patient remained free of asthma until a mild attack occurred in August, 1956, following contact with animals and birds at a bazaar. In October, 1956, she had a cold with mild wheezing which cleared spontaneously without the use of antibiotics. Throughout the winter and spring of 1957, she has had no colds or asthma.

CASE 19.—This 12-year-old boy had a history of chronic upper respiratory infections dating back to 2 months of age. All of his life he had had severe colds complicated frequently by otitis media and bronchitis. His tonsils and adenoids were removed at the early age of 22 months because of these repeated infections. Since starting school this child had been absent almost the entire winter of every school year because of severe upper respiratory infections.

Skin tests done before the age of 6 years showed him to be sensitive to pollens, feathers, and house dust. Treatment with these inhalants as well as with an autogenous vaccine, first prepared in 1950, did not improve his condition. He continued to have crippling recurrent upper respiratory infections. Because of his lack of improvement, cultures were taken from the nose, throat, and sputum in September, 1955. *Micrococcus pyogenes* var. *aureus* (hemolytic and coagulase positive) was isolated from nose cultures. *Streptococcus viridans* and pneumococci were isolated from throat and sputum cultures. Three autogenous B.A.C.'s were prepared from these cultures.

On Sept. 19, 1955, treatment was begun. Inoculations were given intradermally at four- to five-day intervals for the first few weeks and then continued at two- to four-week intervals. Treatment was continued occasionally thereafter until Feb. 27, 1956, by which time the inoculations had produced excellent results and treatment was discontinued. On June 10, 1956, he developed a mild pharyngitis which responded quickly to symptomatic treatment.

A decided reduction in the frequency and severity of this child's upper respiratory infections occurred promptly after the present treatment was begun. He has attended school normally. During the entire winter of 1956 he did not have any serious

upper respiratory infections. He has continued in good health except for minor colds of short duration throughout the winter and spring of 1957.

CASE 21.—This 4-year-old boy has had frequent colds since infancy. In the fall and winter of 1955 and 1956, he could not stay in nursery school for more than a few days at a time because of recurrent upper respiratory infections, many of which were accompanied by attacks of otitis media.

Treatment was started on April 30, 1956, with pooled stock B.A.C. No. 1. He was given intradermally two injections of 0.02 c.c. at four-day intervals of a 1:5 dilution, then weekly injections of 0.02 c.c. of full-strength pooled stock B.A.C. No. 1 for five weeks. Injections were then given every two to four weeks. Since treatment was started, his colds, although still frequent in the winter and spring months, have become less severe, have been unaccompanied by fever, and have not required antibiotic treatment.

CASE 24.—This 9-year-old boy has had frequent upper respiratory infections since he was 1 year of age. In the fall, winter, and spring months colds would recur every two to four weeks resulting in absences from school of from one to seven days in most instances. Treatment with a standard catarrhal vaccine in 1953 resulted in no improvement.

In September, 1955, he was started on respiratory B.A.C. being given injections of 0.02 c.c. intradermally every four to seven days for two months and thereafter every two to four weeks. During the winter and spring of 1956, he had a few mild colds which cleared spontaneously and did not require his absence from school. He had an attack of acute tonsillitis with fever during this period and was absent for one week. In the fall of 1956, he was absent for three days because of a respiratory infection but has been well since that time—throughout the winter of 1956 and spring of 1957.

SUMMARY

Twenty-five children of ages ranging from 2½ to 14 years were treated with injections of acellular bacterial antigen complex preparations made according to the method of Hoffmann. All of these children suffered from frequent recurrent respiratory infections and seventeen of them had attacks of bronchial asthma associated with infections.

Results were excellent in eight cases, very good in eleven, good in four, good but inconclusive in one, and poor in one case.

Reactions to B.A.C. which occurred in a few instances were mild and were subsequently eliminated by dilution of the antigen.

All twenty-five cases have been under treatment for periods of from eleven to twenty months. In the majority of cases after two or three months of treatment injections were given at monthly intervals for prophylaxis.

CONCLUSIONS

1. Acellular bacterial antigen complex preparations of Hoffmann in our experience are of definite value in reducing the frequency and severity of respiratory infections in children.

2. This new type of antigen complex has been shown to be effective in the treatment of infectious asthma. Its use reduced the frequency and severity of respiratory infections in these children and brought about a reduction in the incidence and severity of asthma following these infections.

3. Acellular bacterial antigen complex preparations in our experience are superior to ordinary cellular vaccines, not only in the stimulation of immunity and rapidity of effective response, but in lack of untoward reactions.

4. No significant side effects have been noted.

5. Acellular bacterial antigen complex therapy has permitted the elimination of antibiotic therapy except in a few instances of acute infection.

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OBSERVATIONS ON THE EXAMINATION OF CHILDREN'S FEET

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IT SHOULD be kept constantly in mind that most parents are understandably concerned over their children's health. This may include observations made by them or their friends as to actual or imagined deformities. Probably in no other aspect of the field of orthopedic surgery is there more difference of opinion than on the treatment of foot deformities and foot disabilities. Considerable disappointment is likely to follow when the principles and dicta laid down in the books do not give satisfactory results in a large percentage of cases. It is the opinion of this author that many who speak with authority are guilty also of "armchair" reasoning rather than speaking from actual knowledge. There is some justification for this because the foot, like other parts of the body, is not easily available for study in its integral parts and as a whole while under the normal stress of physiologic function: that of standing, walking, jumping, and in other positions of weight-bearing. For this reason, most material written on the subject is a matter of opinion rather than fact.

Another factor which confronts the doctor who sees many children in his clinic brought in because of supposed foot deformities or disabilities is that most people working as clerks in shoe stores either have developed strong personal opinions about these disabilities and the proper remedy for same through experience in shoe fitting. Or, owing to the urge to be extremely scientific, which is becoming ever more prevalent, shoe companies frequently give courses in what is assumed to be the "truth about feet." These opinions are usually stated with great emphasis as positive fact. Occasionally these opinions are correct; more often they are not. By the time the parents seek the physician's aid they may be considerably confused and worried, and their concern is justified. Therefore, care should be taken in the foot examination and in instruction to parents.

The most common foot conditions in children brought to the attention of the doctor for advice are:

1. Flatfeet.

2. Internal or external rotation of one or both feet. This means rotation of the entire lower leg as a rule, because rotation of the lower extremity occurs at the hip joint, not in the ankle or at the knee, when the leg is fully extended and in a weight-bearing position.

3. Metatarsus varus, which consists of a convexity of the outer border of the foot and a concavity of the inner border when looked at from above, so that even though the heel may be pointing straight ahead the metatarsals, either the first or all five, angulate inward, that is, medialward. This is sometimes spoken of as a third of a clubfoot. While we usually treat this deformity energetically in the new-

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born infant or the child under 1 year of age, there is some question in my mind whether the time and energy spent are entirely justified, since the condition is very rarely seen in the adult, suggesting that perhaps it tends to correct itself.

4. Clubfoot or talipes equinovarus (often abbreviated to T.E.V.). This is a congenital anomaly, and although there is considerable difference of opinion as to its etiology, most people feel that it is not the result of fetal position and pressure, but rather a failure during the process of rotation of the limb bud in which the foot takes part, some time between the fifth and eighth fetal week in the embryo, and/or a muscular dystrophy involving principally the peroneal muscles and the tibialis anticus. One foot of a prematurely stillborn infant was dissected which gave evidence of definite muscular dystrophy in the peroneal muscles. Inadequate work on this subject, however, gives us no stronger proof at present.

There are other deformities and conditions, but these are the principal ones seen in the children's clinic.

Flatfeet.—The term, pes planus, is taken to mean a varying degree of flattening of the longitudinal arch of the foot. Pes valgoplanus implies, in addition to a flattening of the longitudinal arch, a factor of valgus (sometimes spoken of as an eversion) of the heel and entire foot. Careful observation of children under 30 months of age, when they are barefooted and bearing weight, will readily convince one that at this age there is no longitudinal arch clinically visible in the normal child's foot. Probably the development of a longitudinal arch requires the stimulus of prolonged weight-bearing. I am well aware that this is not an orthodox opinion, and frequently children come to the clinic who have worn corrective shoes almost since they began to walk. The corrections consist of arch supports (referred to in the trade as "arch cookies"), heel and/or sole wedges, and various other corrective modifications applied to the inside *or* outside.

Most of the severely relaxed flatfeet develop from a calcaneovalgus deformity in the newborn infant. This is the precursor of the valgoplanus foot seen after the child begins to walk (Fig. 1, *A* and *B*). It is easily missed unless the foot is actually manipulated and the amount of dorsiflexion is tested by upward pressure on the sole of the fore part of the foot. The deformity becomes quite apparent if this dorsiflexion exceeds 50 to 60 degrees, and the condition should be treated. Casting of the feet is the most successful method in the infant. The feet are held in complete overcorrection (position of clubfoot) and cast in this position. In other words, the foot is in equinus, the fore part of the foot is in varus, with the heel in inversion, and an arch is molded into the sole of the cast during application. The cast is allowed to dry while the foot is held firmly in this position. At completion the sole of the foot tends to face the sole of its mate and is in a rather extreme degree of correction. This cast is left on for a full five weeks (the child's growth rarely permits longer). At that time the foot seems to be overcorrected. However, if the foot is examined about four to five weeks later it will be found that much of the correction has been lost. Ordinarily, therefore, casting is repeated three or four times. By then, if the child is more than 4 months of age, an "in swing" shoe (either a tarsosupinator

or a pre-walker clubfoot shoe, reversing the latter so that instead of getting an outflare effect, we get an inflare effect) can be effectively fitted. The shoes are then fastened to a Denis Browne bar with a V bend in the bar in such a way that the convexity is toward the child. This places the feet in inversion, with the forefoot inswing caused by the shoes, plus a little internal rotation achieved by a proper setting of the foot plates on the Denis Browne bar. Usually this is continued until the child begins to walk.

It is true, of course, that there is a definite flatfoot occurring in children who are beginning to walk and to develop a walking pattern. This may be noted as early as 9 or 10 months, when the child first begins to stand. It is easily noticeable by the time the child is 14 months of age. This type of foot consists of an eversion of the heel plus a pronation (eversion, valgus) of the forefoot, in such a way that the foot is usually turned slightly outward at its forward end and the malleolus more nearly approaches the

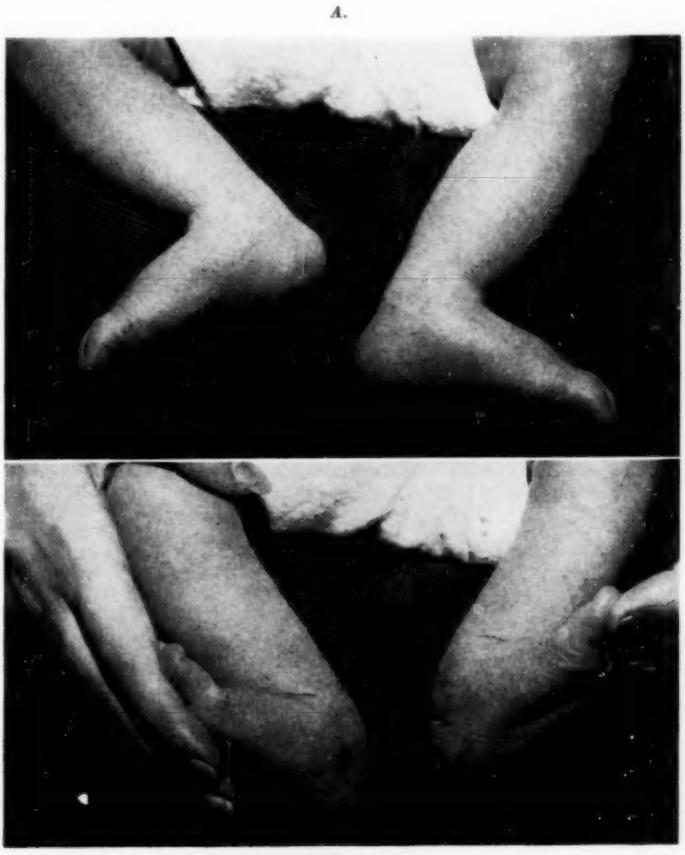
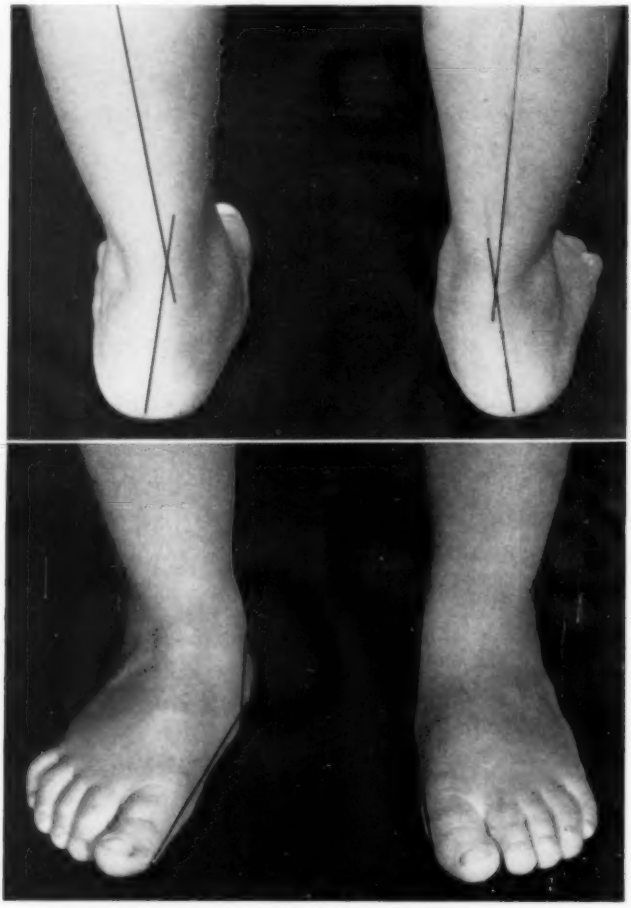


Fig. 1.—Calcaneovalgus deformity. *A*, Feet at rest; *B*, same feet under test.

floor on the medial side. This is a valgoplanus foot (Fig. 2, *A* and *B*). This exaggeration of the valgus factor is most noticeable because, the longitudinal arch is not evident in children until about 2½ years of age.

form of the tarsal bones. These bones in the child under 2 years of age are small calcified "blobs" of cartilage which are somewhat formless and do not fit snugly together. By proper support of the foot in a correct posi-

A.



B.

Fig. 2.—Pes valgoplanus.

Valgoplanus foot occurring in young children is an entity which must be treated if the child is to develop proper foot balance and proper architectural

tion until the child is 4 or 5 years of age, the direction of stress on these bones can be changed and the bony architecture altered according to

Wolff's law. This condition is the result of the calcaneovalgus foot in the infant, mentioned before, and gives rise to the most severe type of relaxed flatfoot in the adult. The usual treatment for deformity is a medial heel wedge. For children up to the age of 2 years it is usually $\frac{1}{8}$ to $\frac{3}{16}$ inch, and for older children it is about $\frac{1}{4}$ inch. If the child is very heavy, particularly after the age of 3 years, it may be necessary to add a Thomas heel extension along the medial border of the heel. This should be at least $\frac{3}{4}$ inch long for small children and longer for older children. It should extend forward to fill the gap between the level surface of the forward part of the sole and the anterior part of the heel, resembling a wedge heel on a shoe. Most shoes supplied with a built-in Thomas heel exhibit only a slight projection on the leading edge of the heel, amounting to little more than $\frac{1}{4}$ inch forward extension from the front edge of the heel. If the Thomas heel extension is necessary at all, a much longer extension than this should be used. This extension is rarely necessary for children under 2 years of age. It provides support for the longitudinal arch, which prevents the shoe from breaking down under the pressure of the flattened arch. Even a steel-shank shoe will frequently break down at this point if the Thomas heel extension is not added. A type of corrective shoe which is even better for the calcaneovalgus foot is the Tarso Supinator, which has a very definite inswing to the forefoot. Occasionally one will find a foot which is a calcaneovalgus foot as far as the heel is concerned, but with some degree of metatarsus varus. For patients with this condition it is best to prescribe a straight-last shoe with a medial heel wedge. A commonly practiced but harmful and unphysiologic shoe correction is the application of the medial heel wedge plus the addition of a lateral sole wedge. It twists the foot about its longitudinal axis in its midportion, forcing the heel in varus (inversion) and the forefoot into valgus (eversion). It seems to cause great unnatural stress in the center of the foot, leading to permanent irreversible damage.

I rarely use insoles or arch supports for children, and when used they consist of a *soft*, rubber arch cookie along the inner side of the longitudinal arch directly under its central portion, just in front of the anterior end of the os calcis. Many of the so-called arch cookies that are put in children's shoes are very hard and cause the child considerable discomfort which results in a limp. Not infrequently, all that is necessary to get rid of the limp and the discomfort, is to remove the supports. Whitman's steel plates both for adults and children are, in my opinion, more uncomfortable than the condition for which they are prescribed and can be tolerated by none but the most stoical.

At this point, it seems wise to add a further note about the application of corrections to the soles and heels of children's shoes. I believe that if correction is needed, it is best applied to high-top shoes. If, for example, a medial heel wedge of $\frac{1}{4}$ inch is applied to an oxford, the foot merely slides laterally down the inclined plane of the inside of the heel cup so that the lateral side of the counter of the shoe bulges outward. This causes the foot to fit into the shoe in such a manner that there is no control of the ankle. Even a high shoe gives relatively little control of the

ankle, but the extension of the upper part around the malleoli when properly fitted and laced actually makes the medial or lateral heel wedge work better because the heel goes into either valgus or varus, depending upon where the wedge is applied. This can be proved by x-ray projections.

In spite of the fact that in most pes planus cases in adults the heel cord is tight when an attempt is made to dorsiflex the foot in varus (supination), one finds that the heel cord is tight only under those conditions. It is felt by some that tiptoe walking should not be prescribed for such patients to assist in arch strengthening. I believe that this is incorrect for the following reasons: The posterior tibial tendon runs downward from the posterior compartment of the leg behind the medial malleolus, inserting, according to Willis,[5] into each one of the tarsal bones except the os calcis. On the opposite side, the long peroneal tendon runs distally from the posterolateral compartment behind and under the lateral malleolus, under the lateral edge of the sole of the foot, and across to insert into the inferior lateral surface of the proximal end of the first metatarsal. When the foot is in standing position (static weight-bearing), there is little assistance from these two tendons in support of the arch of the foot, and most of the work is done by the intrinsic or short plantar muscles of the foot, frequently defective in cases of flatfoot. However, as soon as the heel is slightly raised from the deck so that the foot is plantar-flexed, it appears logical that the posterior tibial tendon, upon tensing, combined with the action of the long peroneal tendon, gives a definite lift beneath the mid-portion of the foot, tending to act as a sling beneath the mid-tarsal region. It is my practice, therefore, to recommend this exercise for at least 150 to 200 steps, morning and evening, for these children by the time they are 2½ years of age and capable of performing tiptoe walking well. It can be observed from behind that, as the patient comes up on his tiptoes, there is a definite tendency to inversion (varus) of each heel. If the child is told to stand not only on his tiptoes but in a slightly pigeon-toed position, this heel varus can be exaggerated. This, of course, is a direct reversal or correction of the deformity of pes valgoplanus in which the heel actually turns out in eversion (valgus).

Such exercises as picking up marbles with the toes or walking on the lateral borders of the feet have given unimpressive results in my experience.

It is my opinion that *good-looking* feet are seldom produced by exercises and corrective shoes. Although by certain operations on the mid-tarsal portion of the foot, such as the Hoke arthrodesis, a better appearance may be achieved, rather stiff painful feet result after the age of about 18 years. For example, if the feet of a child were operated upon at 8 or 9 years of age, five years later when the child was 13 or 14 the report might be: "this is an excellent result. The child has no trouble with his feet and he now has a normal-appearing longitudinal arch." If feet are going to become painful they usually do so after the age of 18 years, and not before, whether treated or not. Many people with decidedly relaxed flatfeet have little or no discomfort. The American Negro in happy circumstances, if he wears sufficiently wide shoes, has very little trouble with his feet even though he stands for long hours at his work and even though his

feet are extremely flat, very wide, and very relaxed.

Internal or External Foot Rotation.—Most cases of internal or external foot rotation are the result of such rotation at the hip joint, and occur in young children, due to the manner in which they sleep. It is common for infants to sleep prone or face-down. In such a position, if the feet are drawn up under the child, the toes are frequently rotated inward and the buttocks extend upward. If the intion, until the child has been walking alone for at least three months. By this time he will have established a normal walking pattern, and usually the internal and external rotators of the hip will have become balanced one against the other. Undoubtedly some of these children have an actual tibial torsion.

I have tried, without consistent success, the usual methods of putting sole and/or heel wedges on the shoes in an attempt to correct this internal or external rotation. Occasionally, improve-

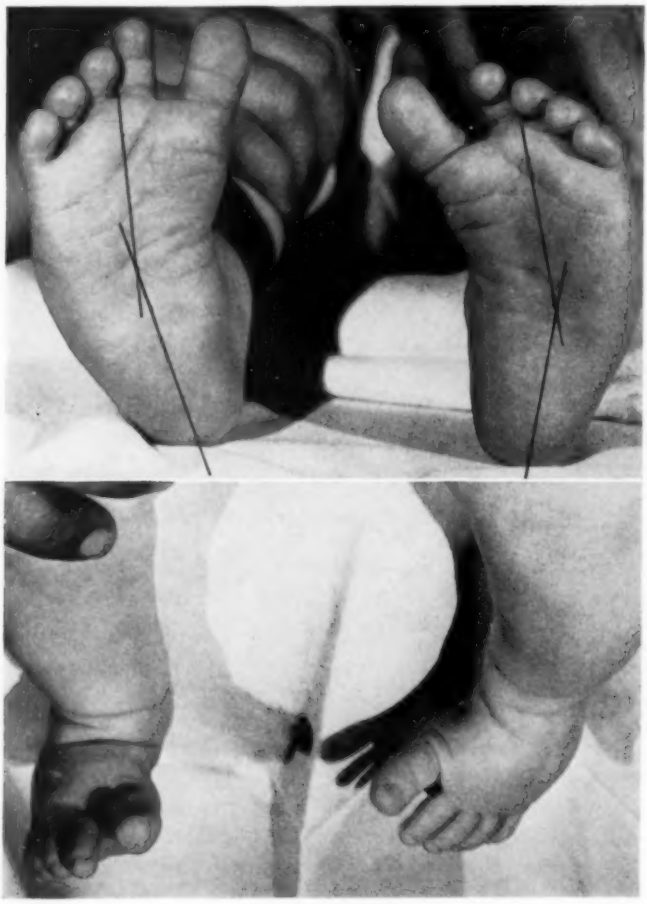
Fig. 3.—Night rotation—Control Board Splint.

fant habitually sleeps in this position over a long period of time, there will be some definite *internal* rotation of the lower extremities. If the child is a "belly sleeper" and lies stretched out at full length, usually the toes point outward and he will begin to walk with some *external* rotation of one or both feet. As a rule, there is no need for concern about the external or internal rotation of the lower extremities, if the hips are found to be normal by clinical and x-ray examinament can be achieved, but usually the method is doomed to failure. Many children who have been wearing "corrective" wedges on their shoes for two or three years are just as pigeon-toed or as "slew-footed" (feet in external rotation) as they were before the correction was started, and the mother is understandably discouraged.

If this in-toeing or out-toeing is not corrected after three or four months of walking, I use a Denis Browne bar or, preferably, an oval piece of

plywood approximately 10 by 8 inches in diameter for young children and about 12 by 10 inches for older children. High shoes are fastened to the board with the heels against the lower edge and the feet toed outward or inward depending upon whether the child is pigeon-toed or slew-footed. Usually the deformity is that of pigeon-toe, and therefore, both heels should be together, with the toes pointing apart at about 60 to 100 degrees (Fig. 3). These shoes, fastened to the splint in this position, are to be worn all night *every* night for approximately four months. The mother must be told that it requires five to six weeks for any change to appear. I prefer the oval plywood board because it is cheaper and because the child can roll

A.



B.

Fig. 4.—Metatarsus varus.

over in bed more easily since it holds the covers up. It is very difficult for the child to turn over when wearing the flat Denis Browne bar.

If, in addition to inward rotation of the lower extremities, the child has some degree of metatarsus varus (forefoot adductus), he should wear an outflare walking shoe during the day to assist in correcting the metatarsus varus. If the inward rotation of the lower extremities in the case of metatarsus varus is not corrected, each step forces the forefoot into varus as the child comes up on the toes. Therefore, a combination of treatment is best used in those cases where there is forefoot varus in addition to inward rotation of the lower extremity.

Metatarsus Varus.—Metatarsus varus (Fig. 4, *A* and *B*), as mentioned before, is a condition that tends to correct itself, and in the very young child it is relatively easy to cure. The mild to moderate cases can be corrected shortly after birth by rather forceful application of firm "holding" casts for several uninterrupted, three-week periods. If the condition is severe, this cast method of correction will have to be continued with more vigor throughout the first four or five months. In some cases, wedged casts after the manner of Kite will be necessary. By the time the forefoot varus is almost entirely corrected, the use of an outflare (pigeon-toe) shoe, or, in the very young child, the prewalker clubfoot shoe, will maintain an adequate amount of outflare to the forefoot and continue the correction achieved by casts. The child should wear these

A.

B.

Fig. 5.—Congenital clubfeet.

shoes night and day until he begins to walk. If at that time the foot is corrected, the child can go into straight-last, normal shoes. Usually if vigorous treatment of the metatarsus varus has been carried out during the first six months, little or no treatment will be needed after that time. Merely *maintaining* the correction until the child begins to walk generally suffices.

In the correction of metatarsus varus, one must be absolutely certain that he is not dealing with a minor degree of clubfoot and must make sure that there is no element of equinus or heel varus.

Congenital Clubfeet.—The treatment of congenital clubfoot (Fig. 5), to be effective, must be thorough, persistent, prolonged, and well understood. Misdirected, delayed, and inadequate treatment results in a recurrence of the deformity in a more resistant degree. For this reason it is recommended that congenital talipes equinovarus be referred to an orthopedist skilled in the treatment of children's deformities. Suffice it to say in this article, that about 90 per cent of uncomplicated clubfeet can be treated successfully by conservative (manipulative and casting) methods. Certain severe cases and the clubfeet occurring in arthrogryposis multiplex may require surgery.

General Comments.—Children who are just beginning to stand and to walk around objects by holding onto them, walk better, in my experience, if they are started in sturdy high shoes with very stiff soles. Slick soles may hinder the child; occasionally the undersurface of the sole should be roughed up with sandpaper or by application of adhesive tape to keep them from being slippery. The average child will actually walk better in stiff-sole shoes than he will in soft-sole shoes. For the occasional child who is just beginning to walk and has definite valgoplanus feet which are the result of untreated calcaneovalgus feet in the newborn infant and for those over 30 months of age who have valgoplanus feet, the Tarso Supinator shoe is often ideal. This shoe tends to bring the forefoot into slight adductus and has a mild medial heel wedge. A somewhat similar result may be obtained merely by using a sturdy high shoe, placing a medial heel wedge with an adequate Thomas heel extension on the shoe. The latter method is preferred for children who, after five to six months of free walking, still persist in an internal rotation deformity of one or both lower legs. Use of a Tarso Supinator shoe in these cases may actually promote internal rotation or even a tendency to metatarsus varus. This has been discussed in a previous section.

Although flat, relaxed feet cannot, by conservative means, be made to have a clinically visible longitudinal arch, they may be excellent functionally.

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SEBORRHEIC DERMATITIS OF INFANTS AND LEINER'S DISEASE: A BIOTIN DEFICIENCY

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IT IS believed that Leiner's disease and seborrheic dermatitis of infants are degrees of the same disease. Leiner's disease, or erythroderma desquamativa, is probably a generalized and greatly intensified seborrheic dermatitis.

The cause of seborrheic dermatitis is not well understood. Some[1] have thought that it is due to an infection with a yeastlike organism, Pityrosporon, others[2] that it is of parasitic origin or is due to hyperactivity of the sebaceous glands. Another explanation is that it results from the lack of a special dietary factor or vitamin which is contained in liver and casein. Reiches[3] believes that it is transmitted directly from an adult, usually the parent, to the infant.

The treatment of seborrheic dermatitis has usually consisted of a low-fat, high-casein diet, liver injections, and local applications of either sulfur, ammoniated mercury, tar, vioform, or selenium sulfide. The treatment of Leiner's disease has been similar to that of seborrheic dermatitis. The same high-protein, low-fat diet is used. Cleansing of the skin is done with Phisohex, and, locally, petrolatum with or without salicylic acid has been applied. Antibiotics usually are necessary for the treatment of secondary infection.

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Recent clinical and experimental work point definitely to a deficiency of biotin, previously called vitamin H, as the cause of seborrheic dermatitis in infants and Leiner's disease. A group of cases treated with biotin are reported here, bearing out this contention.

In reviewing the literature in this regard, it was found that Paul Gyorgy[4] wrote an excellent article on the dietary treatment of scaly dermatoses of the seborrheic type. By feeding rats a diet rich in egg white, a disease was produced which bears the characteristics of a seborrheic dermatitis, similar to the gross appearance in infants called seborrheic eczema. The possibility that egg-white injury in rats might be related to seborrheic dermatitis in man furnished the stimulus for the chemical study[5] of the curative factor, vitamin H, or biotin. Gyorgy's experiments[6] involved about 7,000 rats. The lesions following egg-white injury in rats consisted of intertrigo and confluent pigmented brown scales on the back, resembling cradle cap in infants.

In exceptional cases the disease involved the skin of the whole body of the rat, which resembled the typical exfoliative dermatitis seen in Leiner's disease.

Administration of the specific curative factor even without change in the basal diet of the rat restored normal conditions in two to four weeks. This

specific curative factor was identified as biotin. The best and most potent sources were found in liver, kidney, yeast, and, to a limited extent, in cow's milk.

It is of interest to note that other seborrheic-type lesions can be produced in rats on a diet deficient in pyridoxine and riboflavin, not identical to those due to biotin deficiency although they are all of the scaly, desquamative type.

DESCRIPTION OF TERMS

Seborrheic dermatitis occurs most commonly in infants under 4 years of age. It often begins with cradle cap, a superficial scaly eruption on the cheeks and intertrigo of the axillae, groin, and neck and sometimes around the umbilicus. It is essentially a disease of scaling on an inflammatory base, with very little evidence of vesiculation and oozing.

As a rule, it itches but little, there is no eosinophilia, and skin tests are negative. However, it may be associated with atopic dermatitis and, although not primarily an allergic disease, can and does occur in allergic infants. On the other hand, it may occur as a distinct entity with no other evidence of atopic dermatitis.

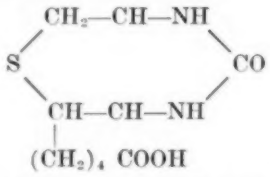
Leiner's disease, which has the characteristics of a widespread seborrheic dermatitis, was first described by Leiner[7] in 1908, when he reported 43 cases. Forty-one of the infants were breast fed and two were bottle fed. Fifteen of these infants died.

The disease begins almost always at the end of the first or the beginning of the second month. It is a peculiar universal skin disease, which consists of a slight inflammation of the whole cutis, a desquamation of the epidermis, and a seborrhea of the scalp.

In uncomplicated cases, there is little itching, no eosinophilia, and no allergic antibodies to be found in the blood. Diarrhea is common in Leiner's disease and is often serious. Secondary infection is frequent and nutrition may become poor. There is often a low serum protein.

BIOTIN

Biotin was first recognized as a growth factor for yeast and isolated by Kögl and Tonnis[8] in 1936 from egg yolk. In 1940, DuVigneaud, Gyorgy, and associates[9] demonstrated that biotin, or vitamin H, was the same as the anti-egg-white injury factor, and isolated vitamin H chemically.[10] Gyorgy had carried out extensive studies on vitamin H as previously described in rats, and DuVigneaud and associates[11] showed that vitamin H was identical with biotin. Harris[12] synthesized biotin in 1943 and gave it the following formula.



The characteristic syndrome of seborrheic dermatitis was produced by Gyorgy in rats fed on a high raw egg-white diet. Rabbit and monkey also showed characteristic dermatitis on high egg-white diet.[14] The presence of a substance, avidin, in raw egg white was found to be the cause of biotin deficiency.

Avidin, a glycoprotein, unites with biotin to form a stable compound which cannot be broken down by proteolytic digestion, but only by heating. Avidin, so combined, prevents the absorption of biotin from the intestinal tract

and provides an experimental way of producing a deficiency of biotin. Avidin is the first known example of an antivitamin.

The requirements of biotin for man are difficult to establish since a large part of the biotin is supplied by the intestinal bacteria,[15] primarily *Esch. coli*. It is postulated that the absence of these bacteria may be responsible in infants for biotin deficiencies. Other sources of biotin are found mostly in liver, yeast, kidney, and egg yolk.

DISCUSSION AND REVIEW OF LITERATURE

The American literature is devoid of any articles describing the use of biotin in seborrheic dermatitis and Leiner's disease. However, the European literature, beginning in 1950, contains a number of articles dealing with the efficacy of biotin in these conditions. It is also evident that Leiner's disease is a much more common disease in Europe than here, and this is probably due to differences in diet. Evidence of this was the marked increase in Leiner's disease after World Wars I and II, when meat, egg yolk, and liver were difficult to obtain in the European countries.

It also became clear that seborrheic dermatitis of the young infant is an illness which bears no relationship to the seborrheic dermatitis of older children and adults.[16] The treatment of seborrheic dermatitis in the older age group with biotin was of no value.

One of the first articles reported was in the Czechoslovakian literature by Palacky and Stryeek[17] in which sixteen cases of Leiner's disease and one case of seborrheic dermatitis were treated. These authors concluded that the favorable response to the treatment with biotin and meat hydrolysates or with a combination of the two seemed to be proof of the deficiency of biotin as the etiological factor in these conditions. In addition, hypoproteinemia and deficiency of gamma globulin were found in these cases.

Svejcar and Homolka,[18] in 1950, reporting from the Children's Clinic in Prague, cured twenty-six breast-fed infants with Leiner's disease by use of biotin. It was they who noted an increase in the number of cases of Leiner's disease after World War II, similar to what had occurred after World War I.

In view of the fact that the children afflicted by the disease were mostly breast fed, they expressed the opinion that the frequency of the disease in their country was caused by a low content of biotin in the mother's milk. This lack was explained by the imperfect nutrition after the war, particularly in such foods as beans, peas, liver, and kidneys.

The serious course of the disease was materially influenced by biotin, which shortened it to a few days. In 1948, not one infant receiving biotin died. The decided action of biotin led them to confirm the assumption of Gyorgy that biotin is the deciding factor in the etiology of seborrheic dermatitis in infants, especially in its most severe clinical form, Leiner's disease.

The amount of biotin found in the blood and urine of children with Leiner's disease was lower on the average, than in normal children. Their patients were treated with daily injections of 0.1 mg., or the nursing mothers were given 4 mg. per day, orally. Amelioration was observed in two to three days and a complete cure in seven to fourteen days. In addition,

penicillin was given to eliminate the secondary infections. During treatment, the biotin excretion in the urine increased as well as the biotin level in the blood.

In five cases of Leiner's disease in bottle-fed infants, the intake of biotin was sufficient, but there was an increased loss of biotin in the urine and feces due to more severe secondary infections and diarrhea. When the infection was controlled, the biotin levels in the urine and feces fell, showing that more of it was retained.

The authors conclude that Leiner's disease in the breast-fed infant is caused by a lack of biotin in the milk of the mother and is sometimes aggravated by secondary infection. In the artificially fed baby, the lack of biotin is caused by general toxic, infective influences which increase the requirement for the biotin and inhibit the possibility of its use in the tissues.

Sara Kokil,[16] in 1954, reported twenty-four cases of seborrheic dermatitis from Germany; twelve of the infants were breast fed and twelve bottle fed; they ranged in age from 2 weeks to 3½ months. Seborrheic dermatitis of the young infant is an illness of its own which bears no relationship to the allergic eczema of infancy or the seborrheic dermatitis of older children and adults. It is a winter disease in Germany, appearing every year from November to April, and is probably due to a lowering of the biotin content in breast milk and cow's milk during that season. The amounts of biotin become insufficient to guarantee normal keratinization. Biotin is a specific against seborrheic dermatitis. Oral or parenteral doses of 5 mg. per day will cure seborrheic dermatitis in two to three weeks. Similar affections of older children are uninfluenced by biotin.

Theelin[19] reiterates the observation that experiments with human beings and animals make one think that the lack of biotin is the cause of seborrheic dermatitis. He describes the favorable results in a case with one injection of 5 mg. of biotin, followed by one week of oral therapy of 2 mg. daily.

Sydenstricker and associates[20] were able to produce a fine scaly desquamation of the skin and a grayish pallor in four adult volunteers fed a diet poor in biotin, of which 30 per cent consisted of egg white. The diet was supplemented by riboflavin and vitamin B complex. The urinary biotin excretion fell to low levels. Treating these volunteers with daily injections of biotin improved the skin and general well-being of the subjects.

In 1951, Martin[21] discussed his results in France. Six cases of localized seborrhea of the buttocks or scalp were definitely improved by oral administration of biotin. He mentions that the dosage of biotin for the infant is unknown. He gives six to twelve daily injections of 5 mg. of biotin. Occasionally, in the severe form, he gives it twice daily. In the milder forms, he recommends oral doses of 2 to 3 mg. per day for several weeks. He refers to Theelin[19] as giving daily intramuscular doses of 5 mg. for fifteen days.

Martin describes his results in four other severe cases. The first infant, breast fed, with Leiner's disease, received daily injections of 5 mg. of biotin for one week, followed by 2 mg. orally, daily for one week. The skin was normal three weeks after the onset of treatment. A second case of extensive seborrhea showed some improvement of the erythema on 3 mg.

orally for five days. The lesions became worse when the drug was stopped. Biotin given intramuscularly for eight doses produced remarkable improvement.

In the third case, widespread seborrhea followed a diarrhea subsequent to Aureomycin therapy for staphlycoccus pleurisy. This case resembles our Case 6, in which the diarrhea responded to vitamin B complex. Martin treated this patient with ten injections of biotin daily, of 5 mg. each; fifteen days later the skin was clear.

In the fourth case, a premature infant with poor weight gain and growth, extensive seborrhea cleared after five injections of biotin, accompanied by excellent weight gain.

Martin finds that approximately fifteen days after biotin treatment, the seborrheic skin desquamates and is replaced by normal skin.

In the treatment of seborrheic dermatitis, Lemke[22] in 1950, stated not only that biotin is indispensable, but that there is a synergism between biotin and vitamin B complex, and that other factors of the B complex are also important in the cure. In one infant, B complex injections produced no improvement until biotin was injected along with the B complex, and a dramatic cure then occurred in four days. In two other cases, the simultaneous injections of vitamin B complex and biotin produced a marked improvement in four days. In two further cases, injections of the nursing mother with biotin and B complex produced dramatic improvement in the breast-fed infant.

To further corroborate the interrelationship of biotin and vitamin B complex, James[23] treated cradle cap with daily oral doses of 1 mg. of riboflavin over a fourteen-day period, with very satisfactory results.

In further studies with the various components of the B complex, Lemke[22] reported that when one child received two injections of biotin plus nicotinamide, there was no improvement until oral B complex and oral biotin were given afterward for fourteen days. Using panthothenic acid and biotin injections, there was improvement in another case, but improvement was most marked when the mother was given liver injections. In four other children, vitamin B_6 was given alone. There was improvement in two of these cases. Biotin was then given in conjunction with the vitamin B_6; two patients were cured, one improved, and in one there was no improvement. Lemke concludes that seborrheic dermatitis is due to an absence of both biotin and the total vitamin B complex. He treats his patients with three injections of 5 mg. of biotin two days apart, plus one ampule of B complex at the time of each injection, both of which were given either to the breast-fed infant or to the nursing mother. His investigations are of further interest in that he demonstrates that liver, which is a good source of biotin, gives no definite results in seborrhea when fed to these infants. This is probably because the infant is unable to separate biotin from liver. However, when the nursing mother was fed 150 grams of cooked liver or kidney for ten days, or 1,500 grams of liver in three to five days, the skin lesions of the breast-fed infant healed in approximately eight days. One kilogram of liver contains 2 mg. of biotin, and this, according to Lemke, should be sufficient for complete improvement of Leiner's disease in

eight days, when ingested by the nursing mother. He demonstrated that nursing mothers were able to cure their breast-fed infants completely by receiving only two 5 mg. injections of biotin. Evidently, small doses of biotin injected in the nursing adult produces biotin for the nursing infant as well as vitamin B complex.

Petrocini and Debernardi,[24] reporting from Italy in 1954, treated seven cases of Leiner's disease and five cases of seborrheic dermatitis in infants with biotin, with excellent results. Three cases of atopic dermatitis failed to respond. In four cases, their doses intramuscularly were 5 mg. daily for six to eleven days. In eight cases, they used 10 mg. of biotin orally, daily, for twenty to thirty days. They found parenteral therapy more effective than oral therapy.

In view of this array of material on the use of vitamin B complex and biotin in the treatment of seborrheic dermatitis and Leiner's disease, several patients were treated with these drugs.

CASE REPORTS

The patients were treated at Children's Hospital of Los Angeles, in private practice, and one case was reported from the Orange County General Hospital. The striking results that were obtained in this group of cases were convincing evidence that a deficiency of biotin was of prime importance in the causation of these two diseases.

The first six cases of seborrheic dermatitis were treated with injections of vitamin B complex, with moderate improvement. Subsequently, biotin* was given, which was even more effective.

*Biotin was supplied by Hoffmann-La Roche Inc., Nutley, N. J., in 5 mg. tablets for oral use and 1 c.c. ampules of 5 mg. each for parenteral use.

Seborrheic Dermatitis Treated With Vitamin B Complex.—

CASE 1.—M. G., male, aged 1½ months, had a rash for one week, with diffuse scaly erythema of scalp and face and intertrigo of axillae and navel. He was being fed evaporated milk and rice cereal. Treatment consisted of an Alacta formula, 10 per cent sulfur ointment, and 1 c.c. of Lederplex intramuscularly, with marked improvement in one week.

CASE 2.—L. P., male, had onset of rash at 2 months of age. There was seborrhea of scalp in the postauricular area. Creases of the groin and axillae were erythematous. The infant was treated with Nutramigen, local sulfur ointment, and 1 c.c. of Lederplex intramuscularly given on four occasions. Very definite improvement was seen after each injection.

CASE 3.—L. L., male, developed a rash at 6 weeks of age. There were seborrheic dermatitis of face and shoulders, scaliness of scalp and eyebrows, and erythema of axillae. He was on evaporated milk formula. Treatment consisted of sulfur ointment, skimmed milk, and 1 c.c. of Lederplex intramuscularly. There was marked improvement in skin eruption.

CASE 4.—H. U., male, at 1½ months of age had diffusely crusted lesions on scalp and rash on back and face. He was treated with Sobee formula and Pragmater at 3 months of age. Seborrhea was still present and the axillae were still erythematous. After 1 c.c. of Lederplex intramuscularly, the skin showed definite improvement.

CASE 5.—N. M., male, had seborrheic eruption of face, neck, scalp, and postauricular areas, beginning at 5 weeks of age. He was treated with Sobee formula at 2 months of age, but the rash became worse, with scaling of eyebrows and face and persistence of diffuse erythema. Treatment with skimmed milk, sulfur ointment, and injection of 1 c.c. of Lederplex gave definite skin improvement.

These five cases, where Lederplex was given for a short time only, revealed the benefit of B complex in seborrheic dermatitis. None of these infants was breast fed. The lesions improved, but there was not complete cure in all of the cases.

Another interesting case is reported to show the production of seborrheic dermatitis and diarrhea due to the long-continued use of antibiotics. Diarrhea and seborrhea were benefited partly by vitamin B complex.

CASE 6.—N. D., male, developed *Esch. coli* meningitis at the age of 1 week. He was treated with Chloromycetin, streptomycin, and sulfadiazine for several weeks; then because of the recurrence of the infection, he was given Terramycin and triple sulfonamides orally. While on this regime, he developed a very severe diarrhea. Cultures of the stools were negative for pathogenic organisms. There was no skin eruption, except for a red perianal rash which was resistant to local therapy.

On the belief that this diarrhea was due to destruction of the normal bacterial flora, with resultant vitamin B deficiency, Solu-B injections were given daily. The diarrhea subsided in a few days and the perianal rash healed. Because of the persistence of an elevated spinal fluid cell count and positive Pandy test, the child was treated with streptomycin intramuscularly, which he received for six weeks, and oral triple sulfonamides which he received for three and a half months.

Lederplex injections were given three times a week during the entire period of drug therapy. During this time, there was no diarrhea, but the child developed seborrheic dermatitis of the scalp, axillae, and the postauricular areas. These lesions persisted despite local therapy and Lederplex injections and disappeared only when all antibiotics were discontinued.

Biotin-Treated Cases.—

Nine cases of seborrheic dermatitis and two cases of Leiner's disease were treated with biotin, with good to excellent results. These cases are presented briefly. The amount of biotin given was considerably less than that described in the literature because of the small supply obtained.

CASE 7.—M. M., male, 1 month old, had seborrhea of the scalp and eyebrows, roughness of cheeks, and erythematous denuded areas of the groin and right axilla. The child was given two 5 mg. injections of biotin three days apart, and the skin cleared in five days. This child was being fed an evaporated milk formula.

CASE 8.—F. S., female, 3 months old, had extensive crusted cradle cap. The child was on an evaporated milk formula. One injection of 5 mg. of biotin was given and Pragmatar was applied locally. The scalp cleared in a week.

CASE 9.—S. G., male, 1 month of age, had an erythematous and crusted scalp. The face was rough and scaly. One injection of 5 mg. of biotin was given and the skin improved. At 3 months of age, the scalp was still scaly, but not as severely so, and the child had several bouts of diarrhea.

CASE 10.—R. W., male, at 3 months of age had seborrheic eczema of the scalp, with extensive erythema and denudation of the skin of the neck, axillae, groin, and retroauricular areas. Biotin was given orally, 1 mg. three times a day, for one week. The response to oral biotin was only fair, with persistence of cradle cap, scaliness of the axillae, and dry flaky skin of the back. An injection of 5 mg. of biotin was given at 4 months of age and the scalp and skin cleared.

Diarrhea was present at 4 months of age and recurred at 6 months. The rash reappeared to a slight extent. The diarrhea responded to skimmed milk and the rash to Vioform ointment.

This case is of interest in that it shows a better response to injected

biotin than to oral biotin. It also shows the coexistence of diarrhea and seborrheic eczema.

CASE 11.—J. H., female, was breast fed for one month. At 1½ months of age, extensive scaling of scalp and eyebrows appeared. There was erythema of the axillae and groin. One injection of 5 mg. of biotin was given. Two weeks later the skin was considerably improved. A second injection of 5 mg. was given. The response was good, with only slight residual scaliness of the scalp.

CASE 13.—B. L., female, had onset of rash at 1½ months, with roughness of face, scaling of scalp, redness of axillae and groin, and crusting behind the ears. The infant had been fed an evaporated milk formula. She was given an injection of 5 mg. of biotin at 2 months of age, and the skin improved, but the scalp remained scaly. Diarrhea was present during this period. At 2½ months of age, the skin and scalp became worse, and 1 c.c. of Lederplex was given, with improvement of skin, but not as dramatic

Fig. 1.

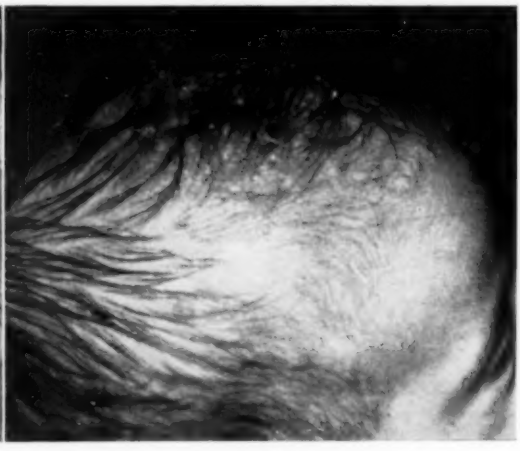


Fig. 2.

Fig. 1.—Typical seborrheic erythematous lesion of axilla.
Fig. 2.—Seborrheic scaling of scalp.

CASE 12.—C. N., male, was on a diet of Lactum, meat, vegetables, and fruit. At 1½ months of age the scalp was scaly and there was angry, erythematous, denuded involvement of the axillae and groin. The child was given 5 mg. of biotin intramuscularly and the diet was changed to Dalactum. One week later the skin showed improvement, with less erythema. Diarrhea was present at this time. A second injection of biotin, 5 mg., was given one week after the first. Two weeks after the second injection the skin and scalp were entirely clear. (Figs. 1 and 2.)

as with biotin. At 3 months of age, a second injection of biotin, 5 mg., was given. The skin improved again and the neck cleared, but the rash recurred after a few days. Two more injections were given a week apart, with improvement of the skin, but again there was recurrence of the rash after a few days. The child was then given daily injections of both biotin, 5 mg., and Lederplex, 1 c.c., for four consecutive days, with marked improvement of the skin and scalp.

CASE 14.—E. T., female, at 10 days of age, had an erythematous eruption

in the gluteal areas, spreading up the back. At 3 weeks of age, there was seborrhea of the scalp, with massive crusting, and moderate crusting of the face, trunk, and postauricular areas. The child was treated with a soybean formula, penicillin injections, saline soaks to the scalp, and Pragmatar ointment. The formula was changed to Dryco. There was slight improvement during the stay in the hospital. (Figs. 3 and 4.)

Fig. 3.

Fig. 4.

Fig. 3.—Scaling and erythema of neck.
Fig. 4.—Scaling, erythematous lesions of face and scalp in seborrheic dermatitis.

After discharge, the child developed diarrhea, and the diet was changed to rice and Nutramigen. Five milligrams of biotin was given intramuscularly and repeated in two days. The formula was changed to skimmed milk, and sulfur ointment was applied locally. Two weeks after the second injection, the skin was clear, except for some redness of the neck and residual crusting behind the ears.

CASE 15.—M. R., male, at 2 months of age had seborrhea of scalp and postauricular areas. Erythema of axillae and groin was present. Stools occasionally were loose. The child was on a meat-base formula because of an allergic sibling. Oral biotin was given daily in doses of 2 to 3 mg. for two weeks, with improvement of the skin, disappearance of the erythema, and minimal residual crusting of the scalp.

Cases of Leiner's Disease.—

CASE 16.—C. B., female, had onset of rash at 4 weeks of age, with cradle cap which gradually became thick and matted. The lesions spread to the chest and back with scaling and oozing. At 7 weeks of age, the entire body was covered with dry yellow flaky lesions and she was admitted to Children's Hospital of Los Angeles. The child had the appearance of a boiled lobster. (Fig. 5.) There was a fine, branny, scaly, dry rash covering a red, angry underlying epidermis which involved all of the skin surface, except the palms and soles. There was no weeping or itching.

The child also had diarrhea, with many green, loose stools. She was first fed soy milk, and the skin became worse. The stool culture revealed Paracolon and the infant was treated with neomycin and triple sulfonamides,

Fig. 5.—Boiled lobster appearance of Leiner's disease.

Fig. 6.

Fig. 7.

Fig. 6.—Diffuse scaly erythematous eruption in Leiner's disease.
Fig. 7.—Scaly desquamation in Leiner's disease.

with little improvement. The diet was changed to skimmed milk and Casec. The diarrhea did not improve and another stool culture showed Proteus.

The skin of the axillae cleared, but the other areas were essentially the same. Lederplex was given orally and followed by three daily injections with no change in the condition of the skin. Two injections of biotin of 5 mg. each were given, three days apart. The diarrhea improved considerably for the first time after these injections, and the skin showed improvement. Vioform ointment was applied. The skin cleared entirely a month after the injections of biotin.

CASE 17.—C. S., male, had onset of erythematous papular rash at 1 month of age over trunk and face. At 2 months of age, the child was fed Mull-Soy and the rash improved, but he began having diarrhea and losing weight. The milk was changed to whole milk. At 3 months of age, the child developed a generalized seborrheic eruption involving the scalp, face, ears, and trunk. At 4 months of age, he was admitted to the Orange County General Hospital with a diffuse erythematous scaly eruption, with considerable desquamation. (Figs. 6 and 7.)

The child was fed a soy milk formula with lamb and rice. He was given injections of penicillin and treated orally with Gantrisin and later with Achromycin.

Biotin was given by injection, 5 mg. every other day for four days, and a salicylic-sulfur ointment was applied to the skin.

Stool cultures were negative for pathogens.

There was marked improvement of the skin eruption about a week after the biotin injections.

CONCLUSION AND SUMMARY

There is evidence, both in the results of the cases reported here and in the European literature, that seborrheic dermatitis and Leiner's disease, which are variants of the same disease, are associated with biotin deficiency. However, the basic requirements of biotin for the infant are unknown.

Nine cases of seborrheic dermatitis and two cases of Leiner's disease showed marked improvement with biotin. The dosages used in our cases, although effective, was perhaps inadequate when compared with the dosage reported in the literature.

The doses recommended, therefore, for Leiner's disease and severe cases of seborrheic dermatitis are 5 mg. of biotin intramuscularly daily for seven to fourteen days. For milder cases, 2 to 4 mg. of biotin orally for two to three weeks are recommended by some authors, and 10 mg. daily for twenty to thirty days by another. The results were better with parenteral than with oral administration of biotin.

Five infants with seborrheic dermatitis were given injections of vitamin B complex alone, with moderate improvement in the skin lesions.

Since there is an interrelationship between biotin and vitamin B complex, and since vitamin B complex enhances the effect of biotin, it may be that better results would follow concomitant daily injections of vitamin B complex along with the biotin.

Feeding the nursing mother with a total of 1,500 grams of liver over three- to five-day periods, or giving her two to four injections of 5 mg. of biotin will seemingly be as effective.

There is also a relationship between the diet of the nursing mother and the incidence of these diseases, as shown by the increased number of cases of Leiner's disease following the wars. The improvement of the diet of both mother and infant as well as the

diminution of breast feeding in this country may account for the infrequency of Leiner's disease.

Foods high in biotin content are liver, egg yolk, kidney, and yeast. These foods are most effective when fed directly to the nursing mother, who can utilize biotin better than the infant.

Biotin is seemingly without value in seborrheic dermatitis of the older child and adult, which suggests a disease of different etiology.

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GIANT CELL HEPATITIS ASSOCIATED WITH HEREDITARY SPHEROCYTOSIS

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FORMS of diffuse hepatic disease of the newborn infant, characterized by the presence of large numbers of giant, multinucleated liver cells, have been described in association with a variety of disorders.[1] The associated disorders include erythroblastosis fetalis, whether due to Rh factor or major blood group (ABO) incompatibility,[2] biliary atresia, and congenital syphilis. In addition, several cases have been reported in which these associated conditions were not demonstrated. Some of the latter cases have shown a familial incidence.[3-6] The etiologic agent in these cases has been variously ascribed to transplacental infection with the virus of homologous serum jaundice,[7] an undetected fetal-maternal blood incompatibility,[5] or a congenital failure in the formation of intralobular bile canaliculi.[8] In one instance, the virus of homologous serum jaundice was considered to have been demonstrated in the blood of both mother and infant by transmission to human volunteers.[7]

In view of the etiologic obscurity of these cases, the occurrence of so-called giant cell hepatitis in an infant with hereditary spherocytosis is of interest. As far as we can determine from the literature, giant cell hepatitis has not been reported previously in association with hereditary spherocytosis.

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CASE REPORT

A. D., a 3-month-old male infant of a Spanish father and an Italian mother, was referred to Jefferson Medical College Hospital from another hospital on Oct. 11, 1956. Born July 17, 1956, the infant's condition at birth was satisfactory. His birth weight was 4.15 kilograms. Slight jaundice was noticed on the fourth day, becoming more intense by the twelfth day. In spite of intensification, the jaundice waxed and waned. The infant took feedings well and gained weight. The stools were clay-colored on several occasions. The urine was consistently dark.

The family history revealed that at the age of 9 years the mother had developed jaundice which varied in intensity and was associated with exertional dyspnea. Laboratory records showed increased erythrocyte osmotic fragility and increased urinary urobilinogen but no bile in the urine. At the age of 17 she underwent splenectomy. Blood transfusions were given before and during the operation. The spleen weighed 715 grams and was typical of hereditary spherocytosis. The liver was not enlarged, and liver biopsy showed no pathological changes other than intense hemosiderin deposition within parenchymal and Kupffer cells. Her recovery was uneventful, and no jaundice has been noticed since the operation. She married at 19 and has had 3 pregnancies. The first and

second children, now 7½ and 3½ years old, had no jaundice. Inquiry into the mother's family history revealed no jaundice of either parent or the siblings.

On physical examination, the infant was active and fairly well nourished but intensely jaundiced. He weighed 5.24 kilograms and was 58 cm. in length. His temperature was 37.4° C., pulse 130. Scratch marks were scattered over the body, but there were no purpuric spots. The lymph nodes were not enlarged. The liver was palpated 5 cm. and the spleen 2 cm. below the costal margins.

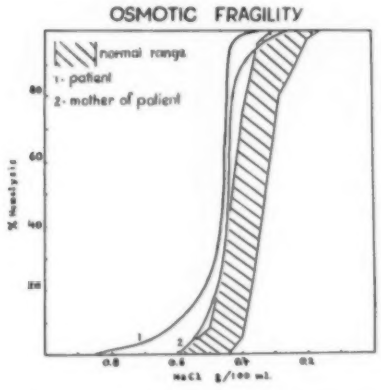

Fig. 1.—The patient's erythrocyte osmotic fragility curve shows increased median fragility and further fragile tailing. The curve from the mother of the patient shows definitely increased fragility even though she has had splenectomy.

Laboratory studies on admission revealed: hemoglobin, 8.28 Gm. per cent; red blood cells, 2,550,000; hematocrit, 22 per cent; reticulocytes, 26.4 per cent; white blood cells, 17,800; platelets, 220,000. The blood smear showed 20 per cent spherocytes. The differential count included 1 per cent metamyelocytes, 1 per cent myelocytes, and 5 nucleated red blood cells per 100 white blood cells. The blood group was O, Rh positive. The direct Coombs and sickling tests were negative. The osmotic fragility was increased (Fig. 1). The hemoglobin analysis revealed 18.5 per cent of alkali-resistant hemoglobin and 81.5 per cent of adult hemoglobin. The test for bile in the urine was strongly positive. The blood urea nitrogen was 19.4 mg. per cent. The serum bilirubin was 16.4 mg. per cent direct, and 25.2 mg. per cent indirect. Thymol turbidity was 4.9 units and alkaline phosphatase 21.85 units. The electrophoretic pattern of the serum was normal. The venous coagulation time was 14 minutes in glass, 48 minutes in silicone tube. Prothrombin concentration was 19 per cent. There was no urobilinogen in the feces.

Studies on the mother showed: hemoglobin, 11.3 Gm. per cent; reticulocytes, 0.8 per cent. The blood smear showed microcytic and hypochromic erythrocytes and many spherocytes. Her blood group was A, Rh positive. The direct Coombs test was negative. The total serum bilirubin was 0.26 mg. per cent. The erythrocyte osmotic fragility was increased (Fig. 1). Liver function tests were within normal limits.

The diagnosis of hereditary spherocytosis was made, and after a preliminary course of vitamin K_1 oxide, splenectomy was performed on the child, Oct. 26, 1956. There was no excessive bleeding during or after the operation, but the postoperative course was complicated by increasing abdominal distention. Death occurred on the seventh postoperative day. Jaundice remained intense throughout the postoperative period.

Pathologic Examination.—The spleen was moderately enlarged, weighing 75 grams (normal 14 grams). Cut surfaces were soft and deep reddish-purple, exuding a large amount of blood. Microscopic examination revealed moderate sinusoidal congestion with numerous areas of hematopoietic activity, which were well demonstrated in splenic imprints stained with Wright's stain. Iron pigment was demonstrated in only small amounts.

Autopsy.—The body was that of a well-developed, slightly undernourished, jaundiced, white male child.

There was flaring of the lower thoracic cage to accommodate a markedly protuberant abdomen having a recent surgical incision in the left upper quadrant. The abdominal cavity contained 850 c.c. of bile-stained fluid. There was edema of the gastrointestinal tract. The liver weighed 230 grams (normal 140 grams). The external surface was finely granular and green. It cut with slightly increased resistance, revealing a dark green surface with indistinct architectural pattern. The gall bladder was normal in size, shape, and position. It contained 10 c.c. of very thick, mucoid, green bile. Careful dissection of the extrahepatic biliary tree failed to disclose intrinsic or extrinsic obstruction. The bile ducts were of normal caliber.

Fig. 2.

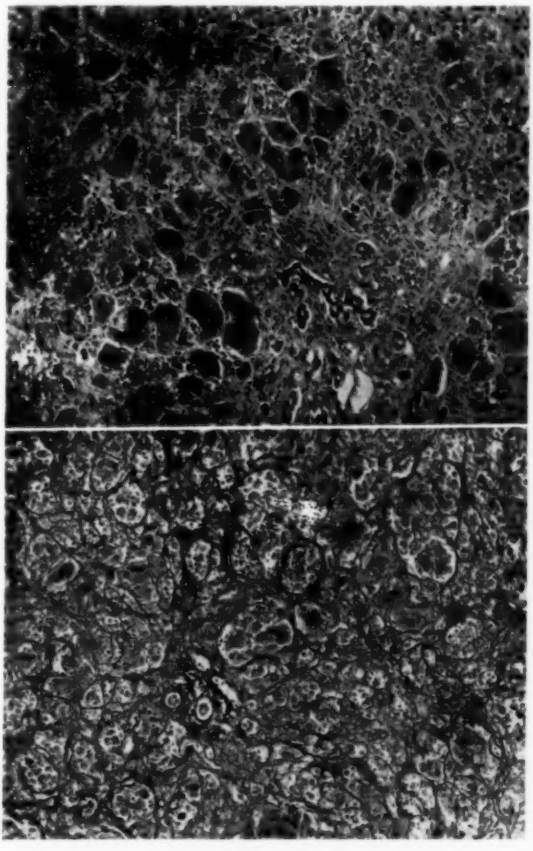

Fig. 3.

Fig. 2.—Liver with large multinucleated hepatic cells, fibrosis, and minimal bile duct proliferation. (Hematoxylin and eosin stains; ×100, reduced ⅓.)

Fig. 3.—There are focal areas of collapse of the reticulum framework with the intervening reticulum surrounding large liver cells. (Wilder's reticulum stain with van Gieson's counterstain; ×100, reduced ⅓.)

The remaining organs were normal except for icterus which was particularly apparent in the kidneys.

Microscopically, there was disruption of the normal lobular pattern of the liver with slight widening of the portal canals. The larger bile ducts were normal in size, and their lumina were free of bile. There was a definite proliferation of the smaller bile ducts located at the peripheries of the portal canals. The striking feature was a transformation of the liver cells into large multinucleated cells with abundant cytoplasm which tended to be basophilic, and contained bile and, infrequently, iron pigment (Fig. 2). Small vacuoles of sudanophilic material were frequently seen in the cytoplasm of these large cells. Groups of giant cells were undergoing degenerative changes, as evidenced by an increased eosinophilia and granularity of their cytoplasm. These cells were usually surrounded by neutrophils. The Kupffer cells contained iron, little bile, and, rarely, fat. Occasional groups of Kupffer cells were found in what appeared to be dilated sinusoids. Focal hematopoietic activity, though present, was not a distinctive feature. The reticulum fibers in some areas surrounded the giant cells (Fig. 3) and in other areas formed a small, tight network.

The renal tubules contained bile casts and were occasionally dilated. The balloon swelling of the epithelial cells of the proximal convoluted tubules seen in other cases of giant cell hepatitis was not noted. The pancreas was normal and contained no deposits of iron. There were no intranuclear or intracytoplasmic inclusion bodies demonstrated in the pancreas, kidneys, liver, or brain.

DISCUSSION

In view of the diagnosis of hereditary spherocytosis, the presence of hepatitis, although suspected, was not seriously considered during life. The extremely high level of indirect serum bilirubin was looked upon as the result of both rapid hemolysis and relative inefficiency of the liver in excreting bilirubin. The high direct serum bilirubin and bilirubinuria were thought to be due to intrahepatic inspissation of bile. Splenectomy was undertaken in the hope of alleviating the hepatic work load. In addition, exploration of the biliary tract was deemed advisable to rule out biliary atresia. The negative flocculation tests are in keeping with previous observations regarding liver function tests in infancy and in the presence of obstructive jaundice.[9, 10]

Whatever the etiology of the peculiar, diffuse parenchymatous change characteristic of giant cell hepatitis, it is quite unlike anything seen in hepatic disorders of adults. It seems, from the recent report by Peace,[1] that the giant liver cell is a nonspecific phenomenon, probably representing a characteristic reaction to diffuse injury of the fetal and neonatal liver. The suggestion of Smetana and Johnson that the giant cell transformation in neonatal jaundice is the result of a congenital malformation is untenable, according to Peace,[1] in view of the fact that some infants recover completely.

In spite of the lack of morphologic changes attributable to hepatitis in the liver biopsy from the mother, the possibility of a placental transmission of serum hepatitis to the infant must be entertained. Indeed, postnatal viral infection, although considered unlikely, is not ruled out. Attempts to demonstrate the virus of serum hepatitis in the maternal serum were not carried out.

While the concurrence of hereditary spherocytosis and giant cell hepatitis may be fortuitous, the reported occurrence of a similar form of hepatic lesion in association with erythroblastosis fetalis suggests a possible relationship between hemolytic disease and the liver disease. There was no evidence of hematologic incompatibility in this case. However, similar forms of diffuse liver disease in the newborn infant have been reported in association with a variety of disorders. In the present state of limited knowledge, so-called giant cell hepatitis in the newborn infant appears to represent a response to a variety of stimuli.

SUMMARY

An infant with hereditary spherocytosis, treated by splenectomy, was found at autopsy to have giant cell hepatitis. The clinical picture was dominated by spherocytic anemia and severe obstructive jaundice. The presence of hepatitis was suspected but not seriously considered during life. The possible etiologic relationship between the two conditions is discussed.

We wish to thank Dr. H. Keitel, Head of the Department of Pediatrics, Jefferson Medical College, for permission to publish the case report.

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FAMILIAL FIBROUS SWELLING OF THE JAWS

Report of a Case

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Jones,[1] in 1933, reported the first case of familial fibrous swelling of the jaws in three siblings, 4, 5, and 6 years of age. In 1938, he made a six-year interim report,[2] and 17 years later, in 1950, he, together with Gerrie and Pritchard,[3] reported further observations on these children. In 1951, Caffey and Williams[4] recorded five instances of fibrous swelling of the jaws occurring in two families and also noted another described by Miller. In 1956 Riley, Stuteville, and Brown[5] reported another instance, making a total of ten cases that have been recorded. All of these were described in surgical and roentgenological journals. Nothing has appeared in the pediatric literature. The purpose of this paper, therefore, is to bring this unusual condition to the attention of pediatricians and to report a further instance. Our patient exhibits all of the characteristic features of those recorded with the exception of a positive family history.

CASE REPORT

An 11-year-old Negro boy entered Illinois Research and Educational Hospital with a complaint of bilateral swelling of the jaws (Fig. 1). The swelling had been present for 6 years and was initially noted at the angles of the mandible. There had never been any fever, weight loss, anorexia, pain, dysphagia, or respiratory embarrassment. At no time was there any suppuration or discharge from the mass either externally or intraorally, and no history of trauma could be elicited. The family history was negative. The father was 35 years of age and the mother 33 years; neither had any mandibular involvement during childhood. There were three siblings, 14, 12, and 8 years of age, all of whom were normal. The pregnancy and delivery had been uneventful. Birth weight was 8 pounds, 8 ounces, with no difficulty in the neonatal period. His growth and development were normal, and there were no illnesses except the usual childhood diseases.

The physical examination was entirely negative except for the external appearance of the facies and the intraoral findings. The tongue was normal in appearance, but the mandible was grossly widened, especially the lingual aspect of the symphysis which resulted in a posterior and superior displacement of the soft tissues and tongue. There was no respiratory embarrassment or dysphagia. The speech, while understandable, was somewhat indistinct. The overlying mucosa and gingival tissue was normal. There was no tenderness, pain, or fluctuation present on digital examination. There was no evidence of involvement of the mandibular nerve, sensation being normal throughout its distribution. The

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temporal mandibular joint exhibited normal range of motion. The lymph nodes in the submaxillary area were very hard, nontender, and freely movable. They were variable in size, some being as large as 1.5 by 2 cm. No areas of present or past drainage could be found.

Fig. 1.

The blood showed hemoglobin 15.9; hematocrit 44; white blood cells 10,600 with a normal differential, and sedimentation rate of 8. The urine examination showed specific gravity of 1.020; pH 5.5; albumin, sugar, acetone and bilirubin negative; white blood cells 1 to 2 per high-power field, and no red blood cells. The alkaline phosphatase was 11 Bodansky units, phosphorus 3 mg./100 ml., calcium 4.9 meq. per liter, total protein 8.4 Gm. per 100 ml., albumin 5.9 Gm. per 100 ml., globulin 2.5 Gm. per 100 ml., nonprotein nitrogen 19 mg. per 100 ml., and Kahn and Wassermann reactions negative.

Bone survey of skeleton including pelvis, wrist, long bones, and vertebrae failed to demonstrate any rarefied areas or involvement of any kind. Anteroposterior and lateral views of the mandible showed a marked enlargement and expansion of the medullary portion of the mandible with marked extension in all directions, especially the mentum, body, and angle (Figs. 2 and 3). The tooth structures were distorted. However, the lamina dura could be seen about several of the teeth. The cortex of the mandible was thin with multilocular cystic or rarefied demineralized zones. There was also a minimal involvement of the maxilla. A section from the mandible and a lymph node from the submaxillary group were removed for study. Gross examination of the bone showed the tissues to be firm and gray-tan in color. Microscopic sections revealed a layer of essentially normal cortical bone (Fig. 4 and 5). The remainder of the tissue was composed of fibrous connective tissue containing numerous fibroblasts and several scattered multinucleated giant cells with as many as 12 to 15 rather large nuclei. Gross examination of the lymph node showed a well-circumscribed nodular mass, measuring 2.5 by 1.5 by 1.2 cm. The tissue was gray-brown to yellow-tan. The cut surface revealed well-circumscribed nodules that were tannish-brown in color. Microscopic examination showed some mild distortion of the architecture by marked dilatation of the subcapsular and central lymphatic spaces, many of which contained considerable amounts of eosinophilic homogeneous fluid (Fig. 6). Some reticuloendothelial cell hyperplasia was present. The remainder of the stromal elements appear edematous, dividing the lymphatic tissue which contains numerous prominent germinal centers into several islands.

DISCUSSION

The onset of this disease usually occurs between the ages of 1 to 5 years and is manifested by progressive, painless bilateral enlargement of the jaws. The facial appearance

Fig. 2.—Frontal view showing expansion of the mandible and multilocular cystic appearance.

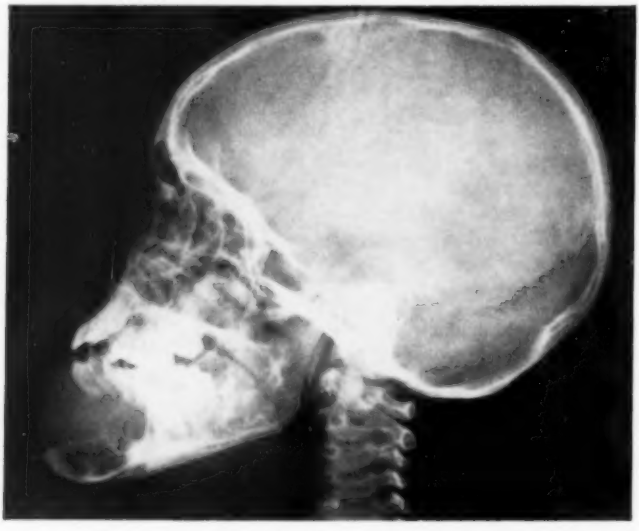

Fig. 3.—Lateral view of mandible showing multilocular appearance.

of these children is remarkably similar. Because of the swelling of the lower jaws the skin of the face is stretched and this in turn retracts the lower lids, resulting in an "eyes raised to heaven look" that Jones so descriptively called cherubism.

The alveolar swelling is usually quite remarkable and may extend lingually to such a degree that the floor of the mouth is reduced to a mere groove and the tongue is displaced superiorly and posteriorly. The appearance and size of the tongue

Fig. 4.

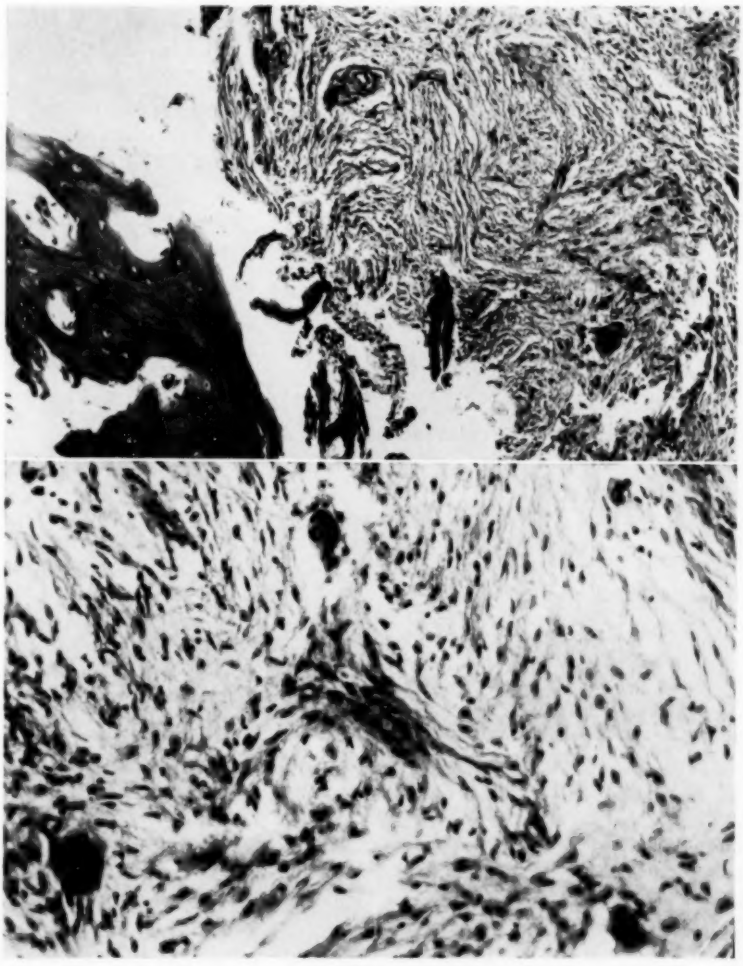

Fig. 5.

Fig. 4.—Photomicrograph of bone marrow biopsy of mandible showing fibroblasts and multinucleated giant cells. (Low power.)

Fig. 5.—Photomicrograph of bone marrow biopsy showing fibroblasts and multinucleated giant cells. (High power.)

are normal; however, mechanical difficulties such as respiratory embarrassment and speech impediment may result from the lingual displacement.

Dentition in the mandible is usually disturbed in some way. The teeth may be ectopic, malformed, missing, or loose. Dentition in the maxilla, on the other hand, is usually normal.

These children characteristically show enlarged, firm, nontender, and freely movable cervical lymph nodes limited to the submaxillary group. In the reported cases, these nodes appear after the facial swelling has become evident. They usually regress after 3 to 5 years. They never suppurate or exhibit a purulent discharge. It may be, as Jones originally postulated, that these nodes are the result of intraoral infection. An alternate explanation might be that possibly the basic pathological process is not limited to the bony mandible and maxilla exclusively but affects the fibrous stroma of the lymph nodes also. It would be difficult, however, to explain the limited involvement, that is, the submaxillary nodes only, on this basis. Jones described the histological appearance of a removed node in one of his patients as showing "fibrous overgrowth and endothelial cell proliferation of the sinuses."[1] There does not necessarily have to be nodal involvement in this disorder. There are no constitutional symptoms associated with the onset or course of this disease. These patients are afebrile, active, exhibit normal growth, and have normal serum values for calcium, phosphorus, alkaline phosphatase, total proteins, and albumin-globulin ratio. Serological tests for syphilis are negative. Sedimentation rate, hemoglobin, and differential smears are normal. Urine examinations are nonrevealing. X-ray survey of the skeletal system, exclusive of the jaws, is likewise negative.

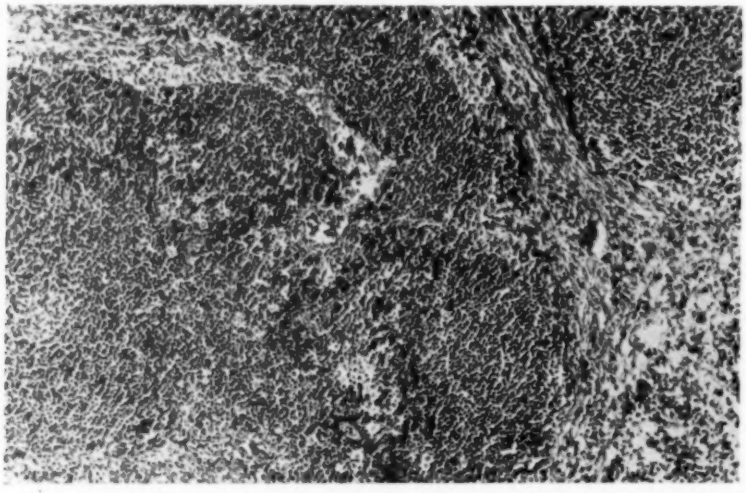

Fig. 6.—Photomicrograph of submaxillary lymph node showing reticuloendothelial hyperplasia.

With the onset of puberty, or shortly before, there is improvement in the appearance of the facies. Usually during this phase new cystic areas cease to appear. However, this is not necessarily so, as new ones may occur simultaneously with the bony reparative process during this time. During this improvement, new bone is laid down in the cystic areas, and consequently the roentgenological picture is that of ground glass in appearance.[4] The facies continues to show progressive change toward normal even after puberty and by middle age may be entirely normal or, at most, show a somewhat prominent mentum.

From the cases reported, it is not possible to determine the hereditary nature of the disease. In one of the families reported by Caffey and Williams[4], the mother, a son, and a daughter were affected while the father and two other sons were normal. On the maternal side, an aunt, uncle, and the grandfather had been affected when they were children. In the second family reported by the same authors, the father and son showed the disease. Ancestors on the paternal side were normal. In the family originally described by Jones, both parents were free from the disease, and the ancestral history was noncontributory. In our case there is likewise a negative family history. The mother of our patient has 17 siblings and, to the best of her knowledge, they are all normal. Our patient has two brothers and one sister who are not affected. We have to conclude that either the changes in the jaws of the ancestors of our patient were so minimal that the condition escaped detection, or that the disorder arose as a mutation de novo. Caffey feels confident that the diagnosis can be made on the basis of clinical and roentgenological findings even in the absence of a family history. There does not appear to be any racial predilection or sex preponderance, although the total cases reported, including our own, show 7 males and 4 females.

Jones originally attributed the condition to multiple dentigerous cysts involving both mandible and maxilla.[1] However, this later proved to be incorrect because the cystic areas do not always contain teeth or remnants thereof and also the areas involved are frequently located in the mandible in locations where teeth are not normally found. The histological sections show fibrous tissue with variable numbers of giant cells of the osteoclastic type.[3] The stroma may vary. There may be a spindle cell fibroplastic type with varying amounts of collagenous tissue. In some areas it may be entirely so and be arranged in interlacing bundles. There may be dilated capillary-like blood spaces lined with endothelial cells. In cortical bone, lacunar absorption may be evident with replacement by collagenous tissue. Large areas of the cortical and medullary portion may be replaced by this dyplastic bone. The microscopic picture is very similar to that of fibrous dysplasia. To add further to the microscopic confusion, Schlumberger[6] pointed out the difficulty of separating fibrous osteoma, osteofibroma, and ossifying fibroma from fibrous dysplasia, and considered these as variants of fibrous dysplasia. Therefore, it may be difficult for the pathologist to make an exact classification of the lesions.

Besides showing a histological picture similar to fibrous dysplasia and these other related conditions, there may be quite a resemblance to giant cell tumor of bone.[3] In fibrous swelling of the jaws, however, the stroma is generally of the spindle cell type and exhibits more collagenous intercellular deposits; also giant cells may be entirely lacking in some areas with only fibrous tissue predominating.[3]

The radiologic appearance depends on the histologic make-up as already described. The fibrous elements cast a radiolucent, cystlike shadow. Prevalence of osseous elements increase the opacity of the lesion and in more mature stages a ground glass appearance results. Spotty areas of calcification may appear, or the entire lesion may present a mottled irregular density. The lesion develops centrally in the bone marrow, and as it enlarges it distends or invades the cortex. The cortex is reduced to a thin, irregular shell, or is absent. Thus the affected bone contains firm rubbery tissue which vary in size from little specks to huge nodules. A multilocular cystic lesion in the roentgenogram results. It should be understood that these are not true cysts with fluid. Fluid occurs only rarely when foci of hemorrhage or degeneration develop.

Our patient presented the typical roentgen features. The bilateral, rather symmetrical, expansion of the mandible is striking, especially in the mental region (Fig. 3). The involvement extends into the angle of the mandible and the coronoid processes. Only the condyles appear spared. The maxilla is involved. However, the lesion in the maxilla appears to be a more diffuse and even rarefaction. Waters' view of the skull will show the involvement of the bony walls of the sinuses to best advantage. The teeth appear ectopic, more so in the mandible than in the maxilla. The lamia dura can be seen.

The differential diagnosis is elaborated in detail below. Caffey[4] and Lewin[12] have helped to clarify fibrous dysplasia of the jaw. Asymmetrical involvement with lesser degree of severity does occur. Polystotic distribution may be present. However, this patient and others cited in the literature have radiographic findings and clinical features which make familial fibrous swelling of the jaw a separate entity.

The differential diagnosis is not difficult if the disease is kept in mind and included in the differential diagnosis of extensive bilateral painless swelling of the jaws having its onset during the preschool period, without associated constitutional symptoms, exhibiting multilocular roentgenological appearance, and with or without a positive family history.

Ameloblastoma at times may be difficult to differentiate. Robinson[7] reviewed 295 cases and found only three under 5 years of age. Out of this group 58 per cent were cystic, 24 per cent were cystic and solid, and 18 per cent were solid. He found that 70 per cent occurred between the ages of 10 and 35 years.[7] This diagnosis must be confirmed or excluded by histological examination.

Another condition that has to be distinguished is multiple dentigerous cysts. Rarely do these tumors cause a generalized enlargement of the jaws. Also these cysts are not commonly found in patients under 5 years of age. Because they are

related to dental follicles, the coronoid processes are spared. On the other hand, in familial fibrous swelling, the coronoid processes are usually extensively involved. These cysts contain one or more teeth with the crown usually facing inward. Fluid is found in them also. These cysts may rupture and discharge.

An endocrine condition that must be considered is hyperparathyroidism with resultant osteitis fibrosa cystica.[8] In this, the earliest lesions may be found in the jaws, but if the mandible were to be involved as extensively as it is in familial fibrous swelling, one would expect lesions to be evident elsewhere in the skeleton. Renal involvement may be found in 75 to 95 per cent of the cases. There are usually constitutional symptoms such as polyuria, polydypsia, anorexia, weakness, fatigue, constipation, and vague pains. The increased serum alkaline phosphatase and calcium, the decreased serum phosphorus, and increased urinary calcium excretion usually point to this diagnosis. In addition to findings in the jaws, x-ray changes may be seen in the metacarpals and long bones. The lamina dura of the teeth may be absent. To exclude this diagnosis, blood chemistries and a skeletal roentgen survey should be done.

Cranial manifestations of fibrous dyplasia of bone is easily ruled out by the absence of dense sclerotic bone at the base of the skull.[9] The roofs of the orbits, the wings of the sphenoids, and the anterior and posterior clinoids may be transformed into sclerotic masses. Consequently, there may be proptosis, protrusion of the malar bones, and deformity of the entire facial skeleton. This is one of the causes of leontiasis ossea. The diploe may be wide, the tables of the calvarium may be thin, and cysts may protrude beyond the outer tables. Other parts of the skeleton show broadening of long bones, thinning of the cortex, and a rarefied trabecular appearance. There may be unilateral skeletal involvement. Skin pigmentation and precocious puberty are also found. Clinically these patients may exhibit headaches, mental deterioration, decreased vision and sense of smell, and obliteration of the paranasal sinuses.

Fibrous osteoma or osteofibroma do not show a cystic appearance on the x-ray,[10] but do show a loss of the normal shadows. The trabeculae of the bone are arranged in a mosaic pattern. Only one case of bilateral involvement has been reported.[10] Bone survey likewise reveals no pathology other than the mandibular lesion. No abnormalities of the blood chemistries are found. Pathologic examination may show giant cells in small numbers. Mature cells with extensive ossification are termed fibrous osteomata, while those that have fibrous tissues and immature bone predominating are classified as osteofibroma or ossifying fibromata.

Giant cell tumor is a slowly growing lesion. In the jaws these are divided into a peripheral type called epulis and an intraosseous type that is found within the body of the mandible. These tumors usually present as a local unilateral growth and on occasion may become cystic.

Other lesions that may have to be considered are[11]: fibrosarcoma, osteogenic sarcoma, metastatic carcinoma from the breast or thyroid, teratoma,

eosinophilic granuloma, and reticuloendotheliosis of the Hand-Schüller-Christian type.

The cause of this disease is unknown. Because of the absence of any inflammatory cells in microscopic examination as well as any clinical evidence of inflammation, it is highly unlikely that the etiology is on an infectious basis. Riley, Stuteville, and Brown[5] noted that the onset of the disease occurs at the same time that resorption of deciduous tooth roots is beginning.[5] They postulated that this process may extend beyond normal limits, that pseudocysts filled with fibrous tissue are formed, and that the improvement during puberty coincides with the end of the deciduous tooth period and with the normal decrease in tooth resorption at this time.

That there are hormonal effects on some types of neoplasms is well known. It seems conceivable that this condition could be a benign neoplasm and that the spontaneous remission during puberty is brought about by hormonal changes taking place at this time. In any event, the exact etiology remains unknown.

Because the natural course of this disease is toward spontaneous remission at the time of puberty or shortly before, active therapeutic measures are not mandatory unless mechanical difficulties such as respiratory embarrassment or speech disturbance are present. If the patient should develop an emotional disturbance because of the cosmetic appearance, this may be an indication to interfere with the course of the disease. Jones, Gerrie, and Pritchard,[3] in their 17-year follow-up of the original cases, report surgical procedures done on these same patients for this reason. The results were excellent. There has been no medical treatment advocated in the cases reported. Because there are no findings, either clinically or histologically, that favor an infectious etiology, antibiotic therapy most likely would be ineffective. Because improvement occurs during puberty, it might be worth while to institute hormonal therapy, either estrogen or testosterone or both, in the course of the disease. Due to the fact that steroids suppress fibrous tissue formation, it would be interesting to see what effect they might have if used very early in the disorder when the changes are minimal. It is possible that they might stop or at least slow down any further deposition of fibroblastic tissue. Because our patient seems very well adjusted emotionally and now has arrived at the period when spontaneous regression is to be expected, no treatment is contemplated. Later, during puberty, if he should show any psychological disturbance that can be related to his appearance, surgery may be considered. In the meantime, he will be followed with cephalometric studies at 4- to 6-month intervals.

CONCLUSION

A child with familial fibrous swelling of the jaws is reported. This is the eleventh instance to be reported. It is characterized by a progressive painless bilateral enlargement of the jaws, having its onset during the preschool years, and is not associated with any constitutional symptoms. The submaxillary lymph nodes are involved in the majority of these cases. Serum calcium, phosphorus,

alkaline phosphatase, total protein, albumin, and globulin are all normal. Skeletal x-rays exclusive of the jaws are likewise normal. The diagnosis is confirmed by the characteristic radiological appearance and biopsy. The only definitive treatment is surgical, and this should be considered only in those patients with mechanical difficulties such as respiratory embarrassment. It is also indicated in those patients who exhibit psychological maladjustment due to their facial appearance or speech impediment.

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RUPTURED OVARIAN CYST IN A NEWBORN INFANT

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OVARIAN tumors are rare in infancy. In 1889 Doran[1] reported bilateral ovarian cysts in a 7-month fetus. Reports on ovarian cysts during the first year of life were made by Beale[2] in 1891, Franqué[3] in 1909, and Neumann[4] in 1927. In 1933 Dodeh[5] reported the delivery of a full-term infant in whom an ovarian cyst was so large, being 12 cm. in diameter and containing 300 c.c. of bloody fluid, that it caused a moderate dystocia. It apparently ruptured during delivery and the baby died. Bulfamonte[6] in 1942 recorded an infant who was distended at birth and in whom roentgenograms of the abdomen indicated a tumor mass. This infant underwent surgery on the thirty-eighth day of life. According to Graves,[7] who successfully operated upon an ovarian cyst in a premature infant in 1951, up to that time only 16 cystic and solid tumors of the ovary in infants under 1 year of age had been published. Two additional reports of ovarian cysts in infants were made, by McIntosh[8] in 1954 and Sherwood[9] in 1956. The youngest newborn with successful surgical treatment was reported by Neikirk,[10] who removed a gigantic follicular cyst of the ovary in a 34-hour-old infant. This review excludes luteinized cysts, which were reported to be more common in infants of diabetic mothers. This condition has been recently described by Ahlvin and Bauer.[11]

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A Negro female infant was born at Research and Educational Hospital on June 15, 1956, to an 18-year-old primipara. The prenatal course was normal. The delivery of a full-term infant was accomplished by low-forceps after a first stage of 19 hours and a second stage of 2 hours. At the time of delivery the child's abdomen was noted to be grossly distended. Physical examination showed a well-developed newborn infant in moderate respiratory distress. No icterus was observed. The respiratory rate was moderately increased, and both diaphragms were elevated. No evidence of pulmonary or cardiac pathology was found. The abdomen showed moderately distended veins, moderate edema of the lower abdominal wall, and considerable edema of the left labia majora. No intra-abdominal mass could be palpated. The liver did not appear enlarged, and the spleen was not palpable. There was shifting dullness to percussion. The rectal examination was negative, and meconium passed normally. Roentgenograms of the abdomen showed a diffuse haziness which was compatible with intraperitoneal fluid.

The hemoglobin was 18.0 Gm. and the white blood count 20,000 per cubic millimeter with 59 per cent neutrophils, 38 per cent lymphocytes, and 3 per cent monocytes. The urine showed a pH of 5.5, protein 1 plus, sugar negative, and microscopic examination negative.

The child was observed for several hours and a slow increase in abdominal distention was noticed, with resultant decrease in effective pulmonary ventilation. The infant passed normal meconium and flatus, but had not urinated. A urethral catheter was inserted when the child was 10 hours

old and some clear urine was obtained. Surgical exploration of the abdomen was decided upon, with a preoperative diagnosis of ascites, cause undetermined.

The child's abdomen was explored through a transverse abdominal incision under general anesthesia eleven hours after birth. Upon entering the peritoneal cavity, a bloody fluid was immediately encountered and a total of 320 c.c. was aspirated. Exploration revealed normal appearing liver, gall bladder, spleen, gastrointestinal tract, and kidneys. The uterus was also normal, as was the left ovary. There was a large unilocular cyst (11 cm. in diameter) arising from the right ovary. The cyst had ruptured which accounted for the free intraperitoneal fluid. The cyst, including the ovary and tube, were excised. The infant made an uneventful recovery and was discharged from the hospital on the tenth postoperative day.

On pathological examination the specimen consisted of an opened cyst measuring approximately 11 cm. in diameter. The outer surface was gray-tan with some petechial hemorrhages, and was smooth and glistening. The inner surface revealed dilated vessels. The thickness of the wall was 0.1 cm. Microscopic sections from the wall of the cyst revealed a fibrous, thick wall. The capillaries were dilated and engorged. No definite lining was present and there were numerous large cells in the inner part of the wall. Sections also revealed eosinophilic cytoplasma with dark, hyperchromic nuclei, resembling degenerated lutein cells. The diagnosis was theco luteal cyst from right ovary.

DISCUSSION

Ovarian tumors in newborn infants are rare. No other infants with this condition, successfully treated on the first day of life, were found in reviewing the literature. The presenting symptoms resembled that of ascites secondary to portal vein obstruction and portal hypertension, an almost uniformly fatal disease in the newborn. In view of this, surgical exploration should be undertaken in ascites of the newborn when such conditions as renal agenesis and Rh incompatibility can be ruled out. If the ascites is found to be due to a ruptured cyst, it will most likely be amenable to surgical repair.

CONCLUSION

The case of an infant with a ruptured ovarian cyst existing at birth is presented, making a total of 19 now reported. It is believed that this is the first instance successfully treated on the first day of life. The clinical picture resembles that of congenital ascites caused by portal vein obstruction. It is our opinion that all newborn infants who have ascites, the etiology of which cannot be determined by medical means, should be surgically explored because of the possibility that a curable lesion may be found.

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DIGITAL NEUROFIBROSARCOMA IN INFANCY

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DURING the past five years, 6 cases of neurofibrosarcoma involving the fingers and toes have been seen at the Children's Hospital in Boston. The seriousness of the original presenting lesion was generally not fully appreciated by the family physician. Most of the cases were erroneously mistaken for a benign blister or a wart and consequently were inadequately treated. If one is familiar with the entity, the clinical picture is so distinctive as to leave little doubt as to the diagnosis. To our knowledge, the entity has not previously been fully described in the literature. The purpose of this article is to report our experience with 6 cases of digital neurofibrosarcoma in infants, describe the clinical picture, and to emphasize the importance of early recognition and prompt surgical excision.

PATHOLOGY

The tumor generally first appears in early infancy as a small pea-sized nodule, and slowly grows over a period of weeks or months. It presents as a nontender, firm, glistening, skin-colored mass fixed to the overlying skin, but it may be movable beneath (Fig. 1). The most common location is the lateral or dorsal surface of the distal phalanx of a finger or a toe. Multiple tumors are frequent. Macroscopically, they are firm, dense, and fairly well circumscribed but are not well encapsulated. On section, they are grayish-white and show a fibrous structure. Microscopically, the epidermis may be hyperkeratotic with areas of acanthosis. The dermis is replaced by tumor consisting of interlacing whorled bands of fibrous connective tissue with an abundance of collagen. These bands tend to interdigitate and appear to meet each other at right angles, sometimes giving a patchwork appearance (Fig. 2). Nuclei vary in size. The cells are spindle or triangular shaped, with palisading. Mitotic figures are infrequent. There is lymphocytic infiltration in the surrounding tissue. Although there is no capsule, transition from the tumor to normal dermis is fairly abrupt, except for fibrous strands extending laterally into the dermis.

ANALYSES OF CASES

In all six of the cases, the tumors presented in the first few months of life. The average age of onset was 2½ months. One was present at birth, two at 1 month of age, and one each at 2 months, 3 months, and 8 months of age. Four were in females and 2 in males. The lesions tended to be multiple. Only two were single lesions. The other four varied from two lesions up to seven separate tumors. The tumors occurred with equal frequency

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Fig. 1.—Dorsal view of a typical neurofibrosarcoma of finger.

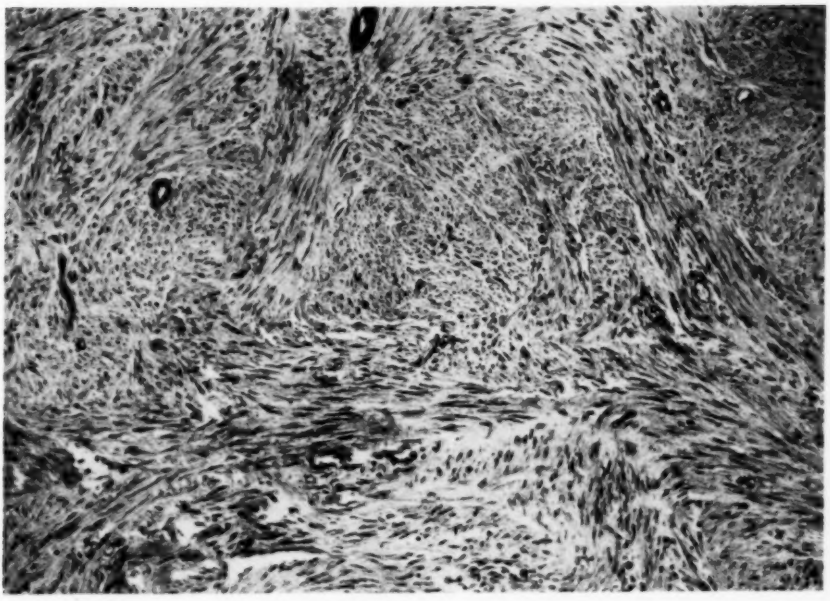

Fig. 2.—Microscopic appearance of interdigitating bands and fibrous whorls (×300; reduced ¼).

on the fingers and on the toes. In all but one of the cases the distal phalanx was involved. They were located either on the dorsal or on the lateral surfaces. In one case involving two toes, the tumors were adjacent with one on the medial surface of the third toe and the other on the lateral surface of the second toe (Fig. 3).

Because the lesions appeared so innocuous, several months generally elapsed before treatment was begun.

A. *B.*

Fig. 3.—*A*, Plantar view of adjacent lesions on toes; *B*, same patient, dorsal view.

The average duration of the visible nodule before treatment was seven months. The earliest treatment was one month and the latest sixteen months after the tumor was first noted. In none of the cases did roentgenograms show bony involvement. Neither did they show any pulmonary or other metastases. However, local recurrences were common. Four of the six cases had local recurrences. Three of these had one recurrence, but the fourth recurred five times and still had tumor without distant metastasis when last seen. In all six cases the initial treatment consisted of local excision. One of these required a skin graft. The four recurrences were either treated again with local excision, with or without skin graft, or digital amputation was carried out. In one case, amputation of two toes, together with part of the metatarsals, was done. One of the cases after four local excisions still had multiple nodules, involving the fourth and fifth fingers of both hands, without regional or distal metastases. The parents were reluctant to have the four fingers amputated.

DISCUSSION

Digital neurofibrosarcomas in infants behave like low-grade fibrosarcomas in adults. They grow slowly, recur locally, and metastasize late. Pack and Ariel,[10] in a review of 39 cases of fibrosarcoma of the extremities, found an average delay of 2.4

years between the onset of symptoms until the institution of adequate therapy. Their local recurrence rate was 56 per cent. Ivins and co-workers,[6] reporting on 78 cases, found 54.5 per cent local recurrences, while Stout[12] found 60 per cent. In our small series of neurofibrosarcomas, the recurrence rate was 67 per cent.

Dermatofibrosarcoma protuberans is closely related to digital neurofibrosarcoma. Pathologically, they are difficult to separate. Dermatofibrosarcoma has a predilection for the anterior surface of the body and rarely occurs on the digits. It, too, is a low-grade malignant tumor, tending to recur locally and not metastasizing until late. It occurs in older children and adults and rarely is seen in infants.

Sclerosing hemangiomas may be difficult to distinguish from neurofibrosarcomas. Gross and Wolbach,[4] reporting on 67 cases, found five on the fingers and two on the toes. Sclerosing hemangiomas are generally flat, have gray, yellow, or pink color, and usually occur in adults.

There is a disagreement in the literature as to the origin of neurosarcomas and fibrosarcomas. Stewart and Copeland[11] state that neurosarcomas constitute the bulk of fibrosarcomas. They feel that the fundamental cell of origin is the Schwann cell. Stout,[12] on the other hand, feels that none of these tumors are derived from peripheral nerves and that the spindle cells are all fibroblasts. He calls all of these tumors fibrosarcoma. We use the term neurofibrosarcoma, because there appears to be microscopic evidence of both nerve and fibrous origin. The tendency to form whorls with bands of interdigitating tissue suggests neurogenic origin, while the abundant collagen is of fibrogenic origin.

These tumors might be called congenital since they occurred so early. One was believed to be present at birth, although it was not excised until 16 months of age. Two others were first noticed at 1 month of age. Fahey and Bollinger[3] in 1953 reported a case of fibrosarcoma of the inner side of the foot noticed at the second day of life. They reviewed the literature on congenital sarcomas and found 35 cases, of which 17 occurred on the extremities. In none of our cases was there history of a similar lesion in a sibling or other relative. Apparently, these are not hereditary tumors. An infectious origin is conceivable since four had multiple lesions. The infant with the tumors on adjacent sides of two toes would certainly suggest an infectious origin. There was no history of trauma or radiation in any of the cases. Like most tumors, the etiology remains obscure.

TREATMENT

Because these tumors do not metastasize early, one is hesitant to carry out early radical treatment. However, the excision must consist of more than simple enucleation, or a recurrence is almost certain to occur. The tumors have fibrous strands extending out beyond the gross tumor. Pack and Ariel[10] feel that in fibrosarcomas recurrence is due to pseudopodium-like extensions of the tumor through its capsule, which persist if excision is limited to decapsulation. Ivins and co-workers,[6] also discussing fibrosarcomas, suggest that even if all the tumor has been excised, the immediate surrounding tissue may be capable of producing malignant change resulting in multiple

primary lesions. Enucleation is obviously inadequate treatment. The other extreme of immediate amputation of a digit or extremity would undoubtedly prevent recurrences but would be needlessly mutilating in most cases. Our recommended treatment is wide local excision with application of a skin graft. With this type of therapy, a small percentage might result in recurrence, but there would still be ample time for amputation. Unfortunately, none of our cases have been followed long enough to be certain of the eventual outcome. The early follow-up suggests wide local excision with skin grafting as adequate therapy. We do not know the effect of roentgen ray. Only one of our cases was managed in this way. Only five treatments of unknown dosage having been given at another hospital. It had no apparent effect.

SUMMARY

1. Neurofibrosarcoma of the digits in infants, though rare, presents a distinct clinical picture.

2. Our experience with six cases is presented.

3. The multicentric origin is suggestive of an infectious (? virus) etiology of this malignant tumor.

4. Early recognition of its specific entity is imperative if cure without radical amputation is to be possible.

5. The preferred treatment in early cases is wide excision with application of a skin graft. In advanced cases, amputation gives the only possibility of a cure.

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THREE CASES OF THE JUVENILE FORM OF AMAUROTIC FAMILY IDIOCY (VOGT-SPIELMEYER DISEASE) WITH ELECTROENCEPHALOGRAPHIC FINDINGS

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SPORADIC cases of the juvenile form of amaurotic family idiocy (Vogt-Spielmeyer Disease) have been reported in the literature in considerable detail, with particular reference to the pathologic findings. The present case report provides a demonstration of the progression in the clinical course of the disease, the changes in the retina, and the electroencephalographic findings.

Familial amaurotic idiocy was first described in infants by the English ophthalmologist, Warren Tay,[1] in 1881, and was further described soon afterwards by the American neurologist, Bernard Sachs.[2] The disease, as it occurs in infants, has since been known as Tay-Sachs disease.

In 1906 and 1907, Vogt[3] and Spielmeyer[4] described the clinical and pathological aspects of the disease as it occurs in the juvenile group. Late juvenile and adult forms have also been described.[5, 6]

Characteristically, the patients appear to be normal children prior to the onset of symptoms. The initial symptoms, which usually begin between the ages of 5 and 8 years, are loss of the previously acquired learning and concomitant diminution of visual acuity. These symptoms progress in a rather protracted course to complete idiocy and blindness. Epileptic seizures may occur early or late in the course of the disease. At the time that loss of acquired learning is noted, other mental and personality changes may be found. The previously normal child becomes apathetic, listless, and disinterested. He may have periods of restlessness and irritability with an intermittent hyperactivity and organic driveness. Hallucinations and delusions are rarely reported, although Levy and Little[7] report a case with well-organized delusions and frightening visual hallucinations. Progressive motor weakness makes its appearance a variable period of time after the initial visual and mental symptoms have become manifest. The motor weakness progresses to a terminal paraplegia and sometimes to a quadriplegia. Characteristically the cherry-red spot in the macular region which is present in the infantile form of the disease is absent in cases which develop during the juvenile period or later. There are reticular deposits of pigment in the retina which are commonly called retinitis pigmentosa. The terminal stage is reached by the age of 18 to 25 years,

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varying with the age of onset. Terminally the patient is blind, quadriplegic, and completely demented. Death usually is brought about by uncontrolled status epilepticus or by intercurrent infection.

For some twelve to fifteen years after the disease was initially described it was thought that all cases of the infantile form of amaurotic family idiocy belonged exclusively to families of central European Jewish extraction. Although this view has since been changed, there is still a greater incidence in Jewish families. The disease is familial rather than hereditary, since the parents of afflicted children cannot be affected by the disease and must be carriers. The inheritance of the disease is dependent upon a recessive Mendelian factor which is present in the heterozygous form in each of the parents, who cannot be affected by the disease and who must be carriers. If one child of the parents is an amaurotic infant, the odds are that one half of the offspring will carry the gene in a heterozygous hidden form and one quarter with the double recessive form will exhibit the clinical disorder.[8] Males are afflicted about equally with females.

REPORT OF CASES

CASE 1.—W. R. R., aged 14 years, white, male. This boy was born of the second pregnancy of a completely healthy mother. The pregnancy was complicated by considerable weight gain and edema of the lower extremities but was otherwise not remarkable. Labor and delivery were uneventful. Birth weight was 8 pounds 12 ounces. The patient was breast-fed for 7 months and was started on solid food at 3 months. He developed normally until the onset of the present illness. He sat up at 7 months, pulled himself to a standing position at 10 months, and, walked at 13 months. He was able to say words distinctly at 1½ years and was speaking in sentences at 2½ years. He did well until he was 7 years old, when the parents noted objective visual difficulty. The visual acuity decreased progressively during the next seven years, and at the present time the patient has only light perception. At approximately 7 years of age the parents also began to notice forgetfulness, inattention, and apathy to his environment. This mental deterioration has also gradually progressed until at the present time he is moderately demented. Two years after the decrease in visual acuity was noted, the patient had his first seizure. These began with turning of the head and eyes toward the left, followed by a tonic spasm of all of the extremities and a generalized clonic convulsion lasting 45 to 60 seconds. After the convulsive movements stop, the patient sleeps for 30 to 60 minutes. Without anticonvulsant medication the patient has as many as six seizures daily; with medication he has about one a month. There have been no hallucinations, and the patient is easily managed.

Family History: Both parents are of German ancestry. There is no known consanguinity. There is no history in either the maternal or paternal families of blindness, mental disease, or convulsions. Another child in the family, a male who is now 18 years old, exhibits no symptoms of the disease.

Physical Examination: The patient had a dull, heavy-lidded expression. He could count to 19, could add 1 plus 1 and 2 plus 1 but not 2 plus 3. His speech was slurred and slow with a juvenile deliberate quality. He could perceive light but not hand movements. The fundi revealed narrowed

vessels with slightly pale disks, particularly at their periphery. The retinae were also pale with reticulate deposits of black pigment more marked peripherally (Fig. 1). The pupils were moderately dilated and equal, and they reacted sluggishly to light both directly and consensually. The patient could not cooperate in attempts to test the extra ocular movements and would not turn his eyes to either side or up or down. The eyes looked straight ahead and a rest there was a fine fixation type of nystagmus. Facial sensation and jaw movement were normal. The muscles of the face, tongue, pharynx, and neck moved normally. There was definite increase in the tone of the muscles of the upper limbs. Motor power was good throughout. The deep tendon reflexes were moderately hyperactive and equal. There was unsustained ankle clonus on both sides. Plantar stimulation resulted in plantar flexion of the toes bilaterally. The sensations were considered to be within normal limits. The gait was wide-based, slightly stiff, and uncertain. This was felt to be due to the blindness.

The general physical examination was entirely within normal limits. There was no hepatomegaly or splenomegaly.

Laboratory Findings: The complete blood count, blood urea nitrogen, fasting blood sugar, and urinalysis were within normal limits. The blood serology was negative. Cerebrospinal fluid pressure was 165 mm. of water. The spinal fluid contained 5 red blood cells, 6 polymorphonuclear neutrophils, and 4 lymphocytes. Spinal fluid protein was 64 mg. per cent; spinal fluid sugar was 59 mg. per cent; spinal fluid serology was negative and the Lange curve was 0111111000. Roentgenograms of the skull were normal and a pneumoencephalogram showed slight generalized dilatation of both lateral ventricles.

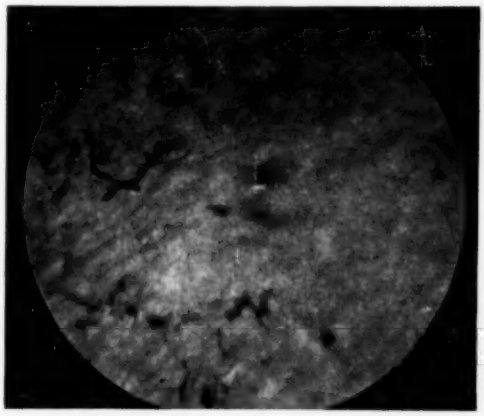

Fig. 1.—Photograph of periphery of fundus of Case 1 (W. R. R.), showing reticulate deposits of black pigment.

CASE 2.—G. W. R., aged 12 years, white, male. This boy, the younger brother of W. R. R., was the third child of the mother. The pregnancy, labor, and delivery were not remarkable. The baby was breast-fed for 9 months, and solid foods were started at 4 months. The development was normal. He sat alone at the age of

6 months, stood alone at the age of 8 months, and walked at the age of 9 months. He spoke single words at the age of 1 year and sentences at the age of 2 years. He continued to develop normally until he was 7 years old, at which time his mother noticed that he was having difficulty in seeing. At this time the mother also noted that the boy's speech was slowed and at times slurred. He stopped learning, although regression in mental status was not recognized until the patient was 9½ years old. At that age he began to have seizures. These began with pain in the head which lasted five to ten minutes. This was followed by tonic rigidity in extension lasting a few seconds and then a clonic convulsion. This persisted for thirty to sixty seconds, and after the attack the patient slept about two hours and was also more irritable than usual for several hours. Since the age of 9½ years the patient has been fretful, hyperactive, and difficult to manage.

Physical Examination: This patient also had a dull, heavy-lidded facial expression. He was somewhat more active and less cooperative than his older brother. He could count up to twelve, but could not add 1 plus 1. His speech was slurred and slow. He could perceive light in either eye but not hand movements. The pupils were round and equal. They reacted to light promptly both directly and consensually. There was a roving type of nystagmus at rest. The fundi were slightly pale, and the vessels were narrowed. There were several small yellowish spots a disk diameter out from the macular region peripherally. Scattered black pigment in a reticulate pattern was noted, but this was much less marked than in W. R. R. There was no cherry-red spot. Sensation over the face and jaw movements were normal. The facial, lingual, pharyngeal, and neck muscles moved normally, and there was no wasting. Tone was increased in all the joints of the lower extremities, most noticeably in the adductors of the thigh on the left. There was slightly increased tone in the upper limbs bilaterally, again more marked on the left. The reflexes were normally active and were equal bilaterally. The plantar responses were flexor and there was no ankle clonus. The coordination was good and sensation normal. The gait was slightly stiff and wide-based, with small, uncertain steps.

The general physical examination was normal; there was no splenomegaly or hepatomegaly.

CASE 3.—S. A. R., aged 9 years, white, female. This is the younger sister of W. R. R. and G. W. R. She was born of the fourth pregnancy of the mother. The pregnancy was uneventful, but labor was difficult. The child was delivered at home; resuscitation was prolonged; and the baby was cyanotic. The head, face, and arms were swollen; but after the first few days the child did well and developed normally. She sat up at 6 months, stood alone at 8 months, and walked at 9 months. She spoke single words at 9 months and talked in sentences at 1½ years. She was toilet-trained at 2 years. She continued to develop normally until she was 7½ years old, when it was noted that she was having visual difficulty. During the past year the child has been in a school for the blind, and the teachers have reported that she has been unable to learn Braille and that she actually does not know as much now as she did some months ago. There has been no gross deterioration, however, and no personality change. She has had two seizures. The attack begins with crying for about two minutes, as if she were afraid. She then seems to lose consciousness and is limp for two minutes and then falls asleep. There are no associated movements of the arms and legs.

Physical Examination: This child appeared brighter than either of the brothers. She was alert and cooperative but shy. She could add 1 plus 1

and 3 plus 1, but not 3 plus 2. Her speech was clear. She could count fingers at a distance of one foot with her right eye, but did this with peripheral vision. She could appreciate hand movements with the left eye. The vessels of the fundi were slightly narrowed and the disks were pale. The deep tendon reflexes were normally active and equal bilaterally. The plantar responses were flexor and there was no ankle clonus. The sensation was normal. The general physical examination was normal, and there was no hepatomegaly or splenomegaly.

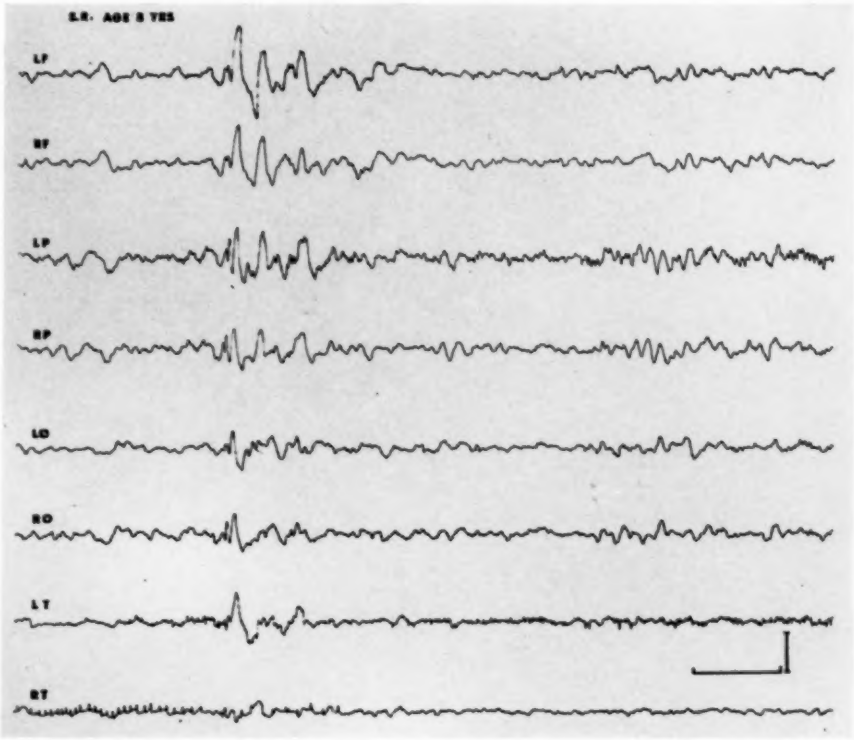

Fig. 2.—Waking electroencephalogram of the youngest child (S. A. R.), showing a burst of generalized slow spike and wave activity.

There was pallor of the retinae, and there were a few scattered yellow spots as well as a very few small scattered black spots. Extra ocular movements were good, and there was no nystagmus. The pupils were round and equal, and they reacted briskly to light both directly and consensually. The remainder of the cranial nerves functioned normally. Motor power and coordination were normal.

Electroencephalographic Findings: The electroencephalograms of these patients were abnormal. They reflect a generalized disturbance in cerebral physiology and have an epileptiform character. The degree of electrographic abnormality correlates well with the clinical severity of the disease in the patients, particularly in regard to the generalized disorganization and slowness of the basic

rhythm. Epileptiform activity (slow spike and wave bursts) was present in each child's electroencephalogram.

The electroencephalogram of the youngest child was diffusely slow with a basic rhythm of 6 to 7 per second predominantly in the parietal regions. There was some generalized slower frequent bursts of generalized spike and wave activity (Fig. 2).

The electroencephalogram of the 12-year-old child (G. W. R.) showed progression in the degree of electrographic abnormality, both in regard to the generalized disturbance and to the amount of epileptiform activity

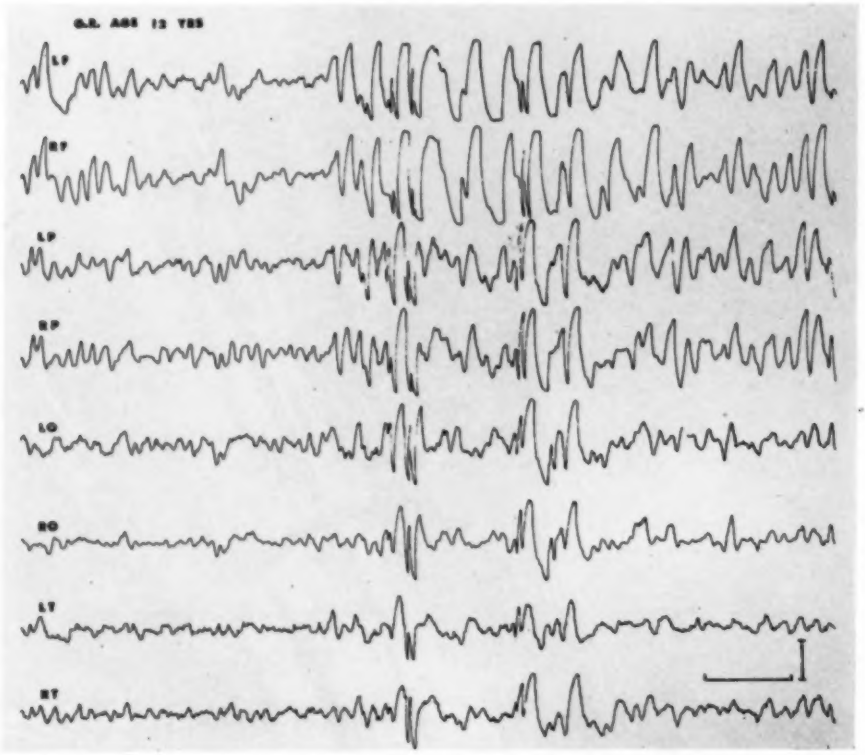

Fig. 3.—Waking electroencephalogram of second child (G. W. R.), showing more active generalized slow spike and wave bursts, and a slower basic rhythm than was seen in the youngest child.

(4 to 5 per second) activity occurring in a random fashion. One generalized spike and wave burst was seen during a one and one-half hour period of recording. A repeat study done six months later revealed progression in the electroencephalographic findings. The record was generally slower, and there were more present. Random waves in the frequency range of 7 to 9 per second were seen in the occipital leads, but the predominant rhythm was an almost constant high voltage 6 to 6½ per second activity chiefly in the anterior leads. Epileptiform activity, consisting of generalized bursts of 2½ to 3 per second slow waves and spikes,

occurred repeatedly throughout the waking record. Constant high voltage spindling in the anterior leads was present during sleep. This activity is considered to be abnormal and is believed to be a sign of upper brain stem or diencephalic involvement[9] (Figs. 3 and 4).

The 14-year-old child (W. R. R.) had a grossly disorganized and slow

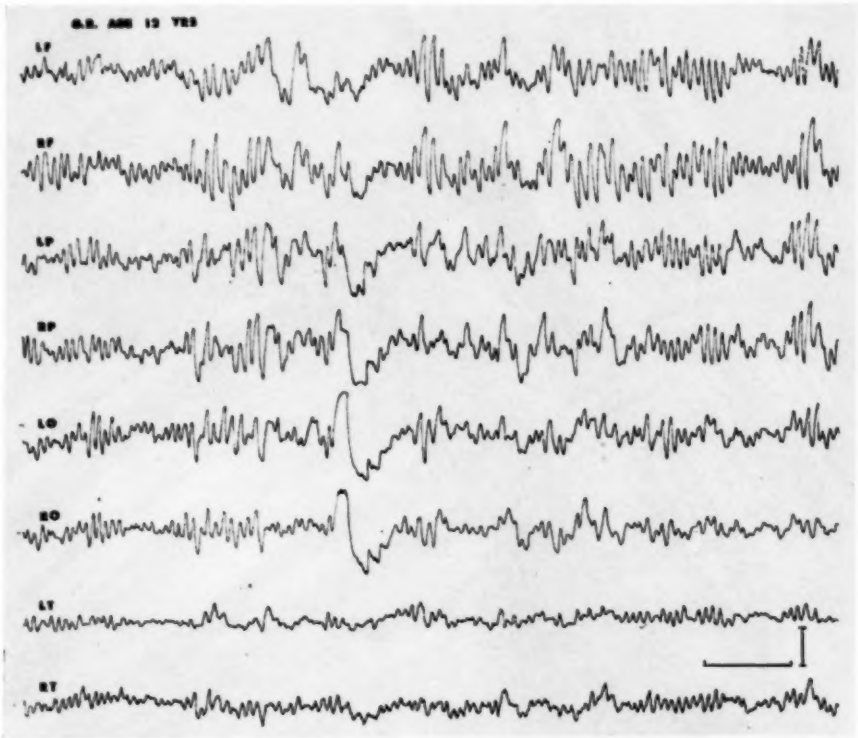

Fig. 4.—Electroencephalogram during sleep of G. W. R., showing constant high voltage spindling, predominantly in the anterior leads.

electroencephalogram with frontal dominant bursts of high voltage 2 per second activity and occasional slow spike and wave complexes (Fig. 5).

Repeat studies of these two patients were essentially the same as when they were initially studied.

Electroencephalograms have been reported in various groups of cerebral lipidoses, and in general these have been diffusely abnormal.[10, 11] The electroencephalogram of the youngest child (S. A. R.) reported was slow when first studied. The primary abnormality, that is, slowing of the basic rhythm, has increased during the eight months she has been followed thus far. Further progression to the grossly abnormal record seen in the oldest child (W. R. R.) can be expected to accompany the clinical progression.

COMMENT

The lipidoses are a group of diseases in which there is a disturbance of lipid metabolism. Among the disease entities which are characterized

by abnormal lipid metabolism are a group which involves the nervous system (infantile, late infantile, juvenile, and adult amaurotic familial idiocy) and a group which usually does not affect the nervous system (Niemann-Pick disease, Gaucher's disease). In this latter group a number of cases seems to be dependent upon the destruction of greater and greater numbers of cells.[12]

Globus, who had been interested in the lipidoses for many years, felt that the disease was a form of abiotrophy or agenesis, that "the nervous system of these children is altered by the

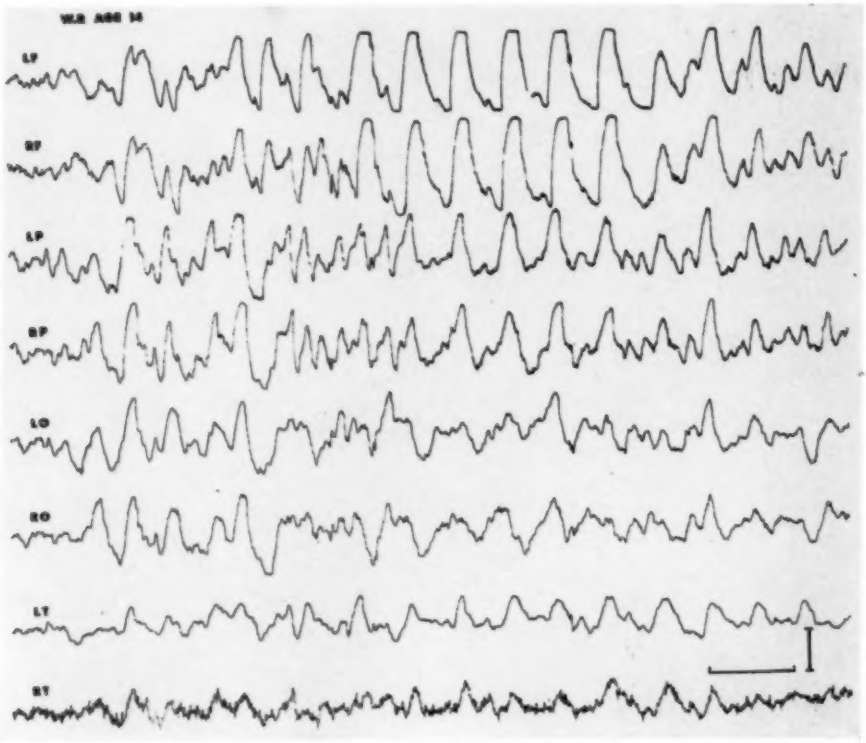

Fig. 5.—Waking electroencephalogram of the oldest child (W. R. R.), showing gross disorganization and diffuse frontal dominant very slow activity.

have been reported in which the nervous system was involved. The varieties which involve the nervous system affect primarily the nerve cells, with accumulation, in abnormal amounts, of a lipid that is normally present. The development of symptoms and progression of the disease

disease at the time of birth, and these cells which are poorly endowed with the means to utilize satisfactory (nutritive) material may at some critical moment in their existence no longer be able to subsist and function properly."[13] The cases reported here are a demonstration of the remarkable

similarity in onset and in clinical progression of the disease in three members of one family. These children were born under normal circumstances, and each developed normally until he had reached an age at which he appeared to have achieved the peak of development and when he began to regress mentally, to lose visual acuity, and to develop weakness, seizures, and muscle atrophy.

The electroencephalographic changes provide added evidence that this is a disease of the brain which is progressive in nature and degenerative in character. The types of electroencephalographic abnormalities which are encountered in the various forms of cerebral lipidosis vary with the age of the onset of the disease. This variation is most likely a function of the level of maturation which the brain has achieved when the disease becomes clinically manifest. Progression in clinical disability is accompanied by increase in degree of electrographic abnormality. This is a functional reflection of the progressively greater numbers of neurons which are being destroyed by the advancing disease process. The character of this abnormality suggests that the disease is degenerative. The electroencephalograms, however, are not specifically diagnostic of cerebral lipidosis, since these findings could represent the electrical response of the cerebral neurons to another disease mechanism which gradually and unselectively destroyed them.

SUMMARY

Three cases of the juvenile form of cerebral lipidosis have been described, the disease occurring in three siblings, a fourth sibling being unaffected. Consanguinity in the parents was not known to be present. The cases provide a demonstration of three stages in the progression of the disease in regard to retinal changes and visual acuity, mental deterioration, and convulsive attacks. The electroencephalograms of these patients are described and provide a further evidence that the disease process is a progressive and diffuse destruction of functioning cerebral tissue.

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CONGENITAL TRACHEOESOPHAGEAL FISTULA IN THE NECK WITHOUT ATRESIA

Report of a Case

Michael Kraus, M.D., and Harvey White, M.D.
Chicago, Ill.

COMMUNICATION between the esophagus and trachea in infancy is a serious condition. Prompt diagnosis and surgical treatment can be lifesaving. The association of atresia of the esophagus with fistula is most common and is adequately described by others in the literature.[1-3] Other congenital anomalies with fistulas also have been reported.[4]

Tracheoesophageal fistula with an intact esophagus is rare, and the whole subject has been very thoroughly reviewed by Ferguson in 1951.[5] Ware and Cross[4] reviewed the English literature and found twenty-six cases of fistula without atresia and added one of their own. Seiber and Girdany,[6] in 1956, reported three additional cases. In our own files, but unpublished, are two cases. In these thirty-two cases all were located in the chest cavity except two, and both of these were located in the neck. One was described by Pinard[7] and Tarnier[8] independently in 1873 and was confirmed by Haight[9] after consultation with the original reference. The other, reported by Imperatori,[10] in 1939, was successfully corrected by surgery. The present case is the third such fistula located in the neck reported in the literature.

From the Departments of Pathology and Radiology, The Children's Memorial Hospital.

D. R., 1 day old, was admitted to The Children's Memorial Hospital on Oct. 11, 1956, because of difficulty in breathing. Delivery was unremarkable, and breathing was spontaneous. Approximately twelve hours after birth severe respiratory distress developed for which a tracheotomy was done.

On admission the infant weighed 6 pounds 1½ ounces; temperature was 100.0°; the cry and color were good; no jaundice was noted. Physical examination of the chest was essentially negative, except for a harsh systolic murmur over the precordium.

Attempts to pass a catheter through each nostril met with obstruction, suggesting bilateral choanal atresia.

Oral feedings of glucose and water given by dropper were tolerated well. At the age of 3 days, jaundice was observed and formula was noted about the tracheotomy tube. A catheter was placed in the upper esophagus, and under fluoroscopic control about 5 c.c. of Iodochlorol was injected through the catheter into the esophagus. The esophagus was immediately visualized, as well as a fistulous tract from the upper esophagus at about the level of the cricoid to the trachea (Fig. 1).

At the age of 4 days, because of inability to suck and regurgitation of dropper-fed formula, gavage feedings were instituted. At the age of 5 days severe jaundice was observed. Feedings were continued by gavage, and work-up for Rh incompatibility started. General condition of the child was poor.

At the age of 10 days, the jaundice began to subside. At 12 days, esophagoscopy was done and considered normal. Continuous suction was necessary to maintain airway because of excessive accumulation of mucus.

Gavage feedings and supportive measures were continued. The condition of the child remained poor. Severe attacks of apnea and cyanosis were not uncommon. On the twenty-third day of life, repeat esophogram with Iodochlorol again revealed the fistulous communication between the trachea and esophagus high in the neck.

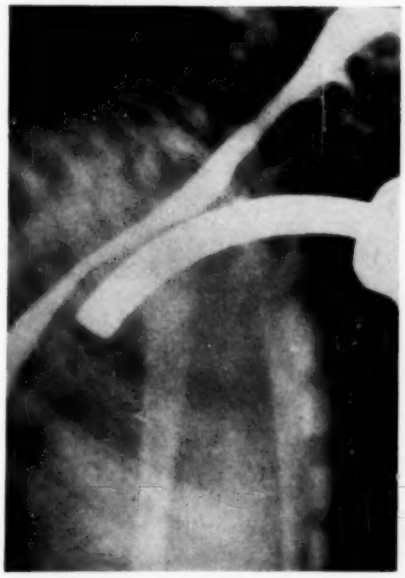

Fig. 1.—Esophogram demonstrating fistulous communication between esophagus and trachea at the level of the cricoid. Tracheotomy tube is well below the fistula.

At the age of 24 days, because of continued regurgitation, a gastrostomy was done. On the twenty-fifth day, during an apneic episode, the child died.

Autopsy revealed a small, poorly nourished and poorly developed infant with marked cyanosis involving the lips, ears, nose, and nail beds. Upon opening the chest, the lungs were found to be markedly congested and consolidated. Numerous subpleural abscesses were present. Investigation of the esophagus and trachea disclosed a communication between esophagus and trachea. This opening was situated just below the cricoid cartilage, was crescentic in outline, and measured 0.5 cm. in diameter. The edges of this opening were smooth, as visualized from the esophageal aspect, and were continuous with the mucous membrane of the trachea (Fig. 2). This communication between the esophagus and trachea was oblique and a probe could be passed easily from the esophageal aspect down to the trachea and then into the main bronchus (Fig. 3). The esophagus was normal in appearance and exhibited a pink, pale mucosa which was of normal diameter throughout. In the trachea there were marked inflammatory changes around the tracheotomy tube and a small amount of foreign material in the trachea and main bronchi.

Fig. 2.

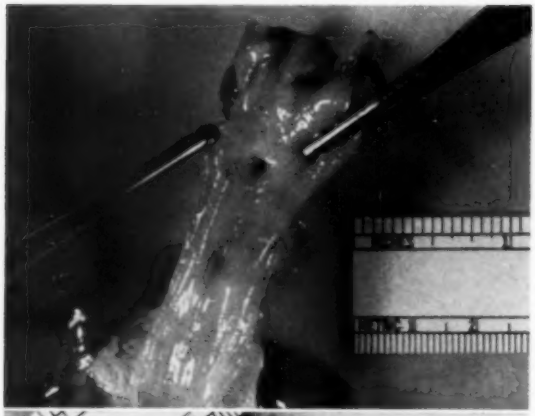

Fig. 3.

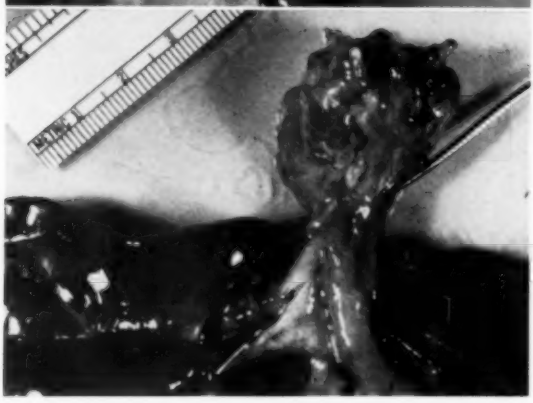

Fig. 2.—Fistulous opening as seen from the open esophagus.
Fig. 3.—Probe passing from the esophagus into trachea into main bronchus.

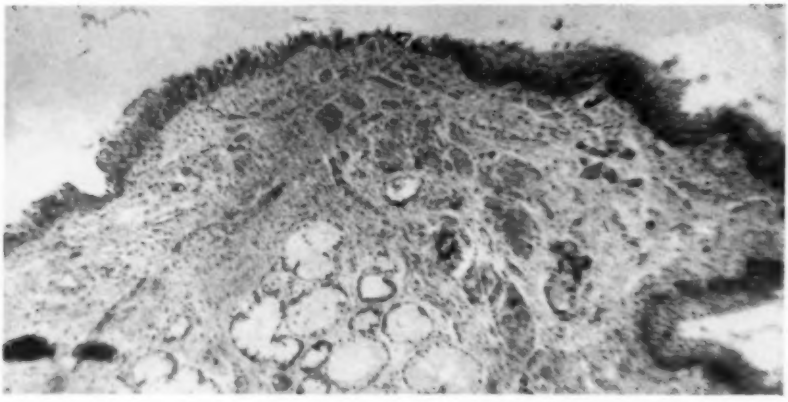

Fig. 4.—Photomicrograph of transition zone of the fistula between respiratory mucosa on the left to squamous cell mucosa of the esophagus on the right.

The microscopic examination of numerous sections confirmed a continuous communication between the esophagus and the trachea. Stratified, squamous epithelium covered the esophageal side of the fistula, with transition from this epithelium to respiratory mucosa as the trachea was approached (Fig. 4).

A large interauricular defect, long patent ductus arteriosus, peritonitis, congestion of the liver, edema of the brain, and bilateral choanal atresia were the other significant gross anatomic findings.

SUMMARY

A rare type of tracheoesophageal fistula in the neck is reported. Surgical repair could not be done in this case because of the general debility of the patient.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS was the first Children's Medical Center admission of this 6-year-old white girl from upper New York State, with complaints of jaundice and pruritus since birth.

The child was noted to be jaundiced at birth. By 2 days of age, the jaundice had increased and the child had developed difficulty in swallowing, but no diagnosis was suggested and the patient was discharged at 4 days of age, with the mother. Both parents were thought to be Rh negative, but the major blood groups were not known.

During the first week at home the infant was listless and took nourishment poorly. At 2 weeks of age she was found to be anemic and was started on a ferrous sulfate molybdum oxide preparation. The parents were concerned because she failed to gain, her jaundice did not clear, and she had a tendency to scratch her skin. She was constipated at this time.

The infant was followed closely by her doctor after her third month of life because she had foul, greasy, bulky, and frothy stools following administration of an enema for constipation, a protuberant abdomen, and no weight gain. He made a tentative diagnosis of celiac disease. The continuing jaundice and pruritus were believed to be due to a persistent neonatal hepatitis. Many changes of formula, including Mull-Soy, goat's milk, Similac, and a celiac diet, were given, with gradual improvement in the appearance of the stools and a moderate weight gain.

During the second year of life the patient had unexplained elevations of temperature and a poor appetite. Despite these, she gained weight, her stools were more nearly normal, and her hemoglobin was maintained. Jaundice and pruritus continued unabated.

At 2 years of age she was seen in another hospital. The findings there may be summarized as follows: the stools were acholic and bulky but had a normal fat and starch content. The cellular elements of blood were normal, with no evidence of hemolysis. The icterus index was 15 and became further elevated during her hospital stay. The serum protein was 8.3 Gm. per cent, with an albumin:globulin ratio of 6.3:1.9. The van den Bergh reaction of the serum was equivocably positive. No etiological diagnosis was established.

The patient remained at home, with continued itching, unrelieved by testosterone and other medication, dark urine, and stools lighter than normal although otherwise not remarkable.

Her appetite improved, her evening pyrexia disappeared, and, in general, her health was considered good. During the four months prior to her entry into this hospital she developed peculiar fears and temper tantrums.

The child had had the usual infectious diseases, including mumps at the age of 3 years and varicella at 4 years of age. The parents are both living and well. One sibling, aged 7, had a history of purpura and celiac disease. The latter child had lead poisoning and was thought to be slightly retarded in comparison with the patient.

On admission to the hospital, the patient's temperature was 98.6° F., pulse 100 per minute, respirations 22 per minute, blood pressure 140/80 mm. Hg. Her height was 41½ inches, and her weight was 35 pounds.

The patient was a small child, in no acute distress. There was a generalized brownish pigmentation of the skin and a suggestion of it in the hand creases. The skin was dry, leathery, and lichenified with excoriated areas. There was no "clear-cut scleral icterus." The lungs were clear to percussion and auscultation. The liver was palpated two fingerbreadths below the right costal margin, and there was a firm globular mass just under the xiphoid, which presumably belonged to the liver. No tenderness was elicited. The rest of the physical examination was negative.

The examination of the peripheral blood revealed a hemoglobin of 12.6 Gm. per cent, erythrocytes 4.01 million per cubic millimeter, leukocytes 9.2 thousand per cubic millimeter, with a differential count of polymorphonuclear cells 38 per cent, lymphocytes 38 per cent, and monocytes 4 per cent. The platelets were adequate on the smear. The urine had a pH of 5.0, the specific gravity was 1.017, no bile was present, but the urine urobilinogen was positive at 1.64. The old tuberculin and Hinton tests were negative. The blood chemical values were as follows: nonprotein nitrogen 34.6; calcium 10.2; phosphorus 6.4; fasting blood sugar 106; serum bilirubin 1 minute, 1.95 mg., and total 3.25 mg. per cent; serum protein was 7.35 Gm. per cent, with albumin 5.01 and globulin 2.34 Gm. per cent. The serum alkaline phosphatase was 9.2 units. The thymol turbidity, thymol and cephalin flocculations were all negative. The stool was negative for bile on one examination and positive (2 plus) on a second. The stool urobilinogen was positive at a dilution of 1:32. The bleeding, clotting, and prothrombin times were normal. A chest roentgenogram and a barium swallow for varices were negative.

The father, mother, and child were all group A, Rh positive.

At the conclusion of the above studies, an operation was performed.

DISCUSSION

DR. FARBER.—Once again we go to the adult internist to solve the problems of pediatrics. We are delighted that Dr. Perry Culver has come to discuss this very interesting problem with us today.

DR. PERRY J. CULVER.*—Dr. Farber, I find this case extremely interesting because I am still puzzled as to the diagnosis, and I am eagerly waiting to hear the answer. If what I suspect is the diagnosis, we may get a clue to a similar, puzzling condition in adults.

*Dr. Perry J. Culver is Associate in Medicine at the Harvard Medical School and Assistant Physician at the Massachusetts General Hospital.

I would like first to make a few brief comments on the protocol as presented.

The child was studied at the age of 2 in another hospital, where evidence of considerable Bromsulphalein retention was elicited. I presume this was done with a 2 mg. per kilogram dose, because the thirty-minute serum value is reported. I would like to know what method was used to determine the fat in the stools. There are a number of microscopic techniques that do not show fat properly. The method of mixing the stool with glacial acetic acid, adding a bit of saturated alcoholic solution of Sudan IV, and heating seems to be the only reliable method of determining stool fat by microscopic examination.

To date, so far as I know, no one has ever determined the cause of itching in jaundice. There are many theories. The most plausible theory seems to be that retention of some form of bile salts—such as taurocholic acid or glycocholic acid—might be a factor in the itching, but the administration of bile salts to patients with obstructive jaundice does not necessarily produce itching. The treatment of itching in jaundice is as unsatisfactory as is the explanation of its cause. To date nothing is very satisfactory.

Methyltestosterone was given. This drug occasionally leads to a type of obstructive jaundice associated with itching, and I feel that it is not wise to use it in the treatment of this condition.

The pigmentation described here is similar to that seen in adult patients who have a form of long-standing obstructive jaundice, who eventually become almost Negroid. Their skin becomes thickened, leathery, and lichenified, with much excoriation, and with pigmentation in the palmar creases. We think this pigmentation is melanin, on the basis of one or two cases. I do not believe the pigmentation represents the nonspecific pigmentation which we see with malnutrition. This patient had the typical biliary dysfunction common with this kind of pigmentation.

The patient had no definite scleral icterus and, considering the early icteric index of 15, and later a serum bilirubin of 3.25 mg., both at borderline for scleral icterus, its absence is not surprising.

In this particular child, I assume that the upper border of the liver was essentially at its normal place, and a two fingerbreadths or 2 cm. liver means that it is moderately enlarged.

We have a recorded minor impairment of bile pigment metabolism in that there is a mild retention of the indirect-reacting bilirubin, and also of the direct-reacting bilirubin. I think that, irrespective of the specific gravity of the urine, when you get a urobilinogen positive in a 1:64 dilution, it represents evidence of a significant increase. On one occasion, the stool was negative for bile. I assume that this means biliverdin. You would not find bilirubin in a child's stool, by the age of 6, if there were no diarrhea. The transit time of the stool through the bowel is such that the bilirubin is converted to biliverdin, and probably further to urobilinogen and urobilin, so that the absence of bilirubin in the stool does not mean anything. On the other hand, the stool urobilinogen is positive at 1:32. The estimation of stool urobilinogen is a gross estimation, but the presence of urobilinogen in the stools certainly indicates that this patient does not have complete obstruction of the biliary tree, which is a very

important observation. Even though the stools were light, and have been described as acholic in the past, we can say that this patient does not have complete obstruction. The presence of increased levels of urobilinogen in the urine suggests that bilirubin is getting into the biliary tree; yet it may not get any farther, because you may have obstruction of the biliary tree with a cholangitis. You then find an elevated urine urobilinogen associated with febrile episodes, such as the patient had a few years before she came to this hospital. The presence of urobilinogen in the urine, thus, does not completely rule out obstruction to the biliary tree, but the presence of urobilinogen in the stool does seem to rule it out.

The normal prothrombin time provides a fairly good measure of the synthetic function of the liver and also suggests that the output of bile salts and bile pigment was sufficient to promote the absorption of vitamin K. In obstructive jaundice, where insufficient emulsifying agents enter the intestine, impaired absorption of vitamin K will occur and a prolonged prothrombin time will result.

Here, then, is a 6-year-old child with continuous mild jaundice, skin pigmentation, good hepatocellular function but mild impairment of the excretory function of the liver on testing, by Bromsulphalein excretion. There is evidence to suggest that there is not complete obstruction to the biliary tree.

What is this child's disease?

This brings us to the big problem of differentiating so-called "surgical jaundice" from "medical jaundice."

By "surgical jaundice" we mean obstruction due to stone, carcinoma, stricture, cysts, pancreatitis, and other rare forms. I think that, for the sake of discussion, we can divide surgical jaundice into five parts.

The first group is composed of the congenital lesions of the biliary tree. These obviously come to mind in any child who becomes jaundiced at birth or shortly thereafter. Dr. Ladd and Dr. Gross comment on the fact that children with congenital atresias of the biliary tree may not become jaundiced until two to three weeks after birth, so the absence of jaundice immediately after birth does not rule out congenital atresia. They emphasize that, in congenital atresia, the jaundice is persistent and the stools always acholic. In such cases, the jaundice is more severe than in the present case. Thus, I believe we can eliminate the usual type of congenital atresia of the biliary tree.

Second, if the child had had evidence of pancreatic fibrosis leading to poor bile and inspissation of the biliary tree, I think that she would not have recovered from this digestive difficulty that appears to be celiac disease; she would have been much sicker or, perhaps, dead, by the age of 6. So I think we can eliminate that condition.

Third, pancreatitis giving rise to biliary obstruction of this duration would manifest itself in a different fashion, and we ought to have evidence for it; if she had enough pancreatitis to cause this prolonged obstruction, I think it would have been quite obvious.

Fourth, we always have to think of hemolytic disturbances leading to the promotion of p a r t i a l l y obstructive stones when we find evidence of an obstructive jaundice in a youngster. All the laboratory tests are negative for evidence of spherocytosis and there was no family history of hemolytic phenomena. The major blood groups have been such that the child does not

have any evidence for blood group incompatibility leading to erythroblastosis.

Fifth: Could she have a rare tumor of the biliary tree? I suppose she could.

By "medical jaundice," we imply the presence of "hepatitis," using the term in its broad sense to include all sorts of inflammatory conditions of the liver, including cirrhosis of various sorts and viral and toxic hepatitis due to various specific poisons.

In adult medicine we have a group of patients who show the laboratory and clinical manifestations of obstructive jaundice. They show other phenomena not brought out on this child, such as a marked elevation of cholesterol and elevations of fatty acids. They usually have a much more marked elevation of alkaline phosphatase than this patient. These individuals who have such evidence of obstructive jaundice have an essentially normal biliary tree, or perhaps one narrowed a little but not enough to be really obstructive; with T-tube drainage these patients produce bile, itching and jaundice disappear, the skin returns to normal, and the tests that are most markedly abnormal (namely, the alkaline phosphatase, Bromsulphalein clearance, bilirubin levels, and serum cholesterol) recede toward normal. If, in such patients, the T-tube is clamped or removed, the condition returns. This condition has been considered by Cecil-Watson in Minneapolis to be cholangiolitic hepatitis. At the New England Medical Center much work has been done on so-called xanthomatous biliary cirrhosis, but we are not sure what that is. Whatever the condition is called, there remains this peculiar group of patients, without much obstruction to the biliary tree, but with evidence of hepatic dysfunction so far as their excretory function is concerned, and with no real evidence of hepatocellular damage.

In considering the broad group of hepatitides, we must ask whether there is evidence of chronic hepatitis. Is this the sort of case that has been described by Dr. Stokes and his group in Philadelphia, and by Dr. Gellis and his group here? As you well know, this particular form of intrahepatic liver disease will often appear early in infancy. It may come from mothers who have never had any clinical manifestations of hepatic disease, but Dr. Stokes showed in one case that the mother was later able to transmit homologous serum hepatitis virus to volunteers. It is assumed, in these cases, that the virus of homologous serum jaundice is circulating in the mother, but it is in a symbiotic state, so that the mother does not manifest overt disease. This virus is probably transmitted through the placenta to the infant, and thus the infant may have a form of homologous serum jaundice prenatally and go on to develop typical cirrhosis. These children manifest the kind of cirrhosis with ascites that is seen in adults, and most of the liver function tests should be abnormal, suggesting hepatocellular disease. However, this child does not have any such manifestation.

A second possibility is, likewise, one described by Dr. Gellis' group, that of prolonged jaundice in infancy. Their paper,[1] in addition to discussing various forms of obstructive jaundice with which you are all familiar and which are more commonly known, mentions a group of vague cases of "inspissated bile," of unknown etiology, with no particular obstruction to the biliary tree, although in many of the cases

there is evidence of fluid imbalance or dehydration. In this case, one wonders if this early difficulty in swallowing, or the celiac state, could have been the etiological agent. This has its counterpart in adults. In such cases, usually in the presence of biliary cirrhosis, there is impairment of bile flow into the gut, a failure to absorb fat-soluble vitamins and fat, with a resulting steatorrhea. If this child had that syndrome, I would expect that the fatty diarrhea would have continued.

In closing, I would like to say that this child probably had celiac syndrome, and that, at operation, a fairly normal common bile duct was found. There may be just a tiny bit of narrowing, if you are looking quite hard for it, but there is no real obstruction and no atresia. She had either the hepatitis that has been described by Dr. Craig, Dr. Stokes, and others, without abnormal hepatocellular liver function tests, or she had this inspissated bile type of syndrome of unknown etiology that has been described by the group here. I am going to take the second group.

DR. SYDNEY S. GELLIS.—I do not know whether Dr. Culver has made any mistakes—because you never know what Dr. Craig is going to come up with at the end of these discussions—except that I think he made one mistake by starting off and assuming he was among friends; you are never among friends here, Dr. Culver.

I think I would agree with the reasoning all the way through. One of the things that interests me is the jaundice present at birth. I can at least say something about this case that Dr. Craig cannot prove or disprove; that is, there must have been something wrong with the baby's placenta. I do not think we see babies born with jaundice unless the mother's circulation is unable, for some reason or another, to absorb the bilirubin that the baby is forming. I, personally, have encountered one case of the "inspissated bile syndrome" due to erythroblastosis, in which the baby had signs of obstructive jaundice at birth. There have also been two reports from Baltimore of similar cases, with severe hemolysis going on in utero, both with the bilirubin not passing the placenta, so that the baby presents a picture of obstructive jaundice.

I agree pretty much with Dr. Culver's reasoning about neonatal hepatitis. This, again, could present with jaundice at birth but I think it would have to be in a mother who had something wrong with her placenta, so that the baby would be jaundiced at birth. In a case of neonatal hepatitis, on the other hand, there should have been more evidence of cirrhosis than is described. Our patients with severe cases of neonatal hepatitis have done very poorly and quite early in life they began to show marked cirrhosis and signs of liver failure, with ascites and evidence of portal hypertension. Therefore, I would not be willing, on the basis of this child's course, to agree to a diagnosis of neonatal hepatitis. I suspect that this falls into a group of strange diseases that Dr. Craig has been arguing about for quite some time, that is, an abnormality of the intrahepatic ducts which has been described by Dr. MacMahon.[2] Some of these patients have had absence of the extrahepatic ducts as well. Most of the children that we have seen with the absence of extrahepatic ducts and with hyperplasia of intrahepatic ducts died at about 1 or 1½ years of age. When you do see a child who, you

think, has absence of the extrahepatic ducts and who survives as long as this child did, you then suspect that there is something wrong with the intrahepatic ducts, apparently preventing a rapid destruction of the liver. I have seen a few such patients, and most of them have had xanthomas of the skin associated with elevated cholesterol levels. During the period of relatively good liver function, the cholesterol and cholesterol esters rise rapidly and their xanthomas of the skin appear. As the liver undergoes subsequent destruction, the cholesterol falls and xanthomas disappear.

DR. LOUIS K. DIAMOND.—I would like to emphasize what Dr. Gellis said about jaundice at birth. Unfortunately, too often the physician sends in a patient like this with the statement that jaundice was present at birth. What he often means is that jaundice was present when he first got a good look at the baby, some hours after having delivered it. In the cases we have tried to follow in which there was jaundice at birth, I think that in at least three we have found some placental abnormality.

I wonder if we can ignore this statement that there was a peculiar mass under the xiphoid. Should we not consider the possibility of some congenital abnormality of the biliary tree, cystic or otherwise, that would lead to a low-grade, intermittent type of jaundice which might be clear for most of the time and would allow good function but would occasionally obstruct again?

DR. FARBER.—You are thinking of a choledochal cyst?

DR. DIAMOND.—It usually gives more complete obstruction than this, when obstruction does occur.

DR. HARRY SHWACHMAN.—I noticed that Dr. Culver mentioned pancreatic fibrosis and then ruled it out almost immediately. I think he is right in ruling it out, but I do not think I agree with his reasons. He said that the age of the child was one of the factors against it. Children can have this disease with the first clinical manifestations severe enough to call them to the attention of the parents at the age of 10, 12, or even older, before medical aid is sought, so that the mere age of the child does not rule out this diagnosis.

I think it would be more correct to say that the intestinal disturbance here is the "celiac syndrome," since "celiac disease" is a quite specific entity. This child had steatorrhea due to a disturbance of her biliary tract function, rather than the true idiopathic celiac disease.

DR. CULVER.—Although we cannot be sure how good the stool studies are later, the steatorrhea apparently disappeared pretty completely. If it were due to biliary dysfunction, I would not expect the steatorrhea to disappear.

I agree completely that you can have first presenting manifestations of pancreatic fibrosis at a much older age. On the other hand, here is a person at the age of 3 months to 2 years, who is having considerable digestive dysfunction which seems to get better. If it were pancreatic fibrosis it would not behave that way, and for this reason I believe pancreatic fibrosis can be ruled out.

DR. CRAIG.—I might read Dr. Longino's operative note: "After the peritoneum was opened, the liver was

inspected and found not to be enlarged, of normal color, and soft. Exploration of the biliary tree revealed the gall bladder to be small and it contained a small amount of normal appearing bile. The common biliary duct was normal in size. It could be traced from the cystic duct to the duodenum. The hepatic duct was small throughout its entire length but was patent. A

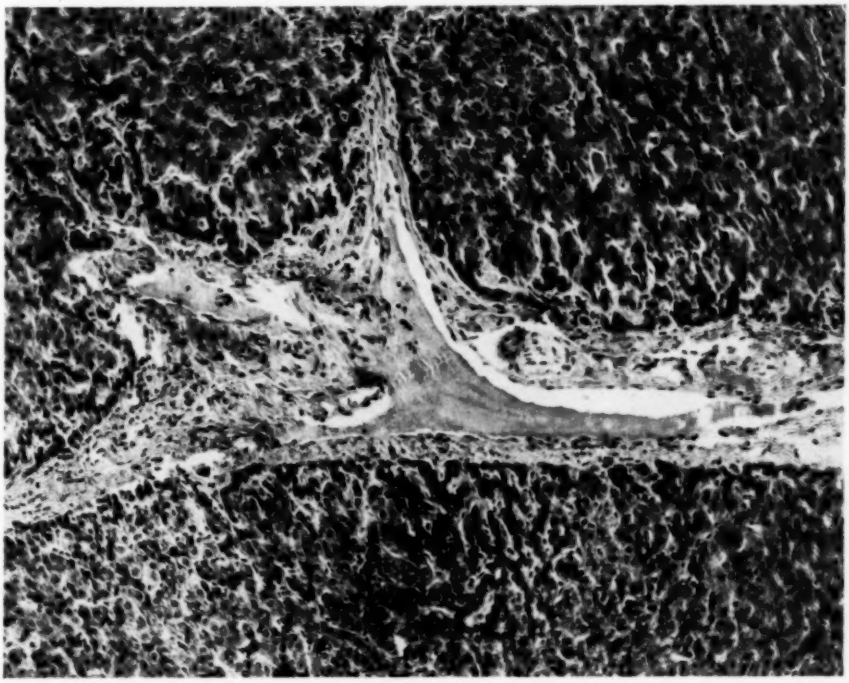

Fig. 1.—Photomicrograph of liver. A typical large portal triad without bile ducts. (Toluidine blue eosin; ×140.)

No. 18 polyethylene catheter was inserted and a good flow of bile was obtained." This flow of bile continued for about three weeks and all were very pleased with this result. However, at that time the bilirubin was as high or higher than it had been before the operation and the jaundice had not decreased. The child then went home and continued to do poorly. It was thought that perhaps a second operation might further elucidate the problem and the child was brought back to the hospital. Her bilirubin ran in the same range, perhaps a little higher (11 mg. direct and 20 total). On the second operation, three months after the first, a quite different picture was found by Dr. Longino. The liver, this time, was grayish-green and was felt to be quite firm. This was a marked change from the previous operation. The hepatic ducts were again explored and while patent up to the liver, no bile was present in the duct. Biopsies of the liver were obtained at both operations from widely separated areas. In both there was a complete absence

of bile ducts (Fig. 1) in the portal areas. In the biopsy at the first operation, no bile stasis was present either in the canaliculus or in the liver cells. In the second biopsy, bile was demonstrated in both areas and there was a slight widening of the portal triads, though there was no change that could be described as cirrhosis. We feel, then, that this case falls into the category of partial absence of the extrahepatic ducts with patent extrahepatic ducts. In comparison with the children who have only atresia of the extrahepatic ducts, such patients have a longer duration of life; they may have extrahepatic duct anomalies, either stenosis or, in some cases, complete atresia. They frequently have elevations in their serum lipid and xanthomas and retarded growth. In one of the cases described,[3] from Dr. Dahl-Iversen's Clinic, no bile stasis was present within the liver cells, which is interesting in view of our findings in the first biopsy in this patient. Dahl-Iversen and Gormsen described two different kinds of "absence of bile ducts," one in which the large ducts are completely absent; in the second group they find that the large ducts are absent, but there are small cholangioles, the smallest radicles extending out into the liver lobules. They find also, as in this case, no cholangitis or pericholangitis. This is one of the reasons, I believe, that these children survive without portal hypertension.

The late Dr. Alwin M. Pappenheimer found a congenital hereditary lesion in a group of mice, which was very similar to this, with proliferation of cholangioles and absence of the larger intrahepatic ducts.

DR. CULVER.—I do not see how you can have a good flow of bile at one time, and three months later, none, with such a lesion.

DR. CRAIG.—Well, I suspect that there may be a few bile ducts in some areas of this liver, but, in the large portion of the liver, I think there must not be.

In children with classical extrahepatic atresia but normal intrahepatic structures, if exploration is carried out at 6 months of age, one will find much bile duct proliferation and fibrosis, but if such an infant lives beyond the usual 1 year, and dies at 5 years of age, often with marked signs of portal hypertension, one may look through many sections of liver before finding bile ducts. Yet fields do exist in such cases where large numbers of bile ducts are congregated. We believe this absence of ducts in large areas is due to a dropping out of bile ducts. It may be that such a failure of continued response, with atrophy of duct structures and concomitant inflammation, may be one of the factors allowing for the long life in such patients.

DR. FARBER.—It is always with great trepidation that anyone disagrees with Dr. Gellis, but I am going to now. You are among friends, Dr. Culver, and, as a sign of that, may I turn over the last word to you.

DR. CULVER.—Thank you, Dr. Farber. All I can say is that I do not think this explains the whole story.

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Medical Progress

THE PEDIATRICIAN AND HIS CHANGING WORLD

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BY THE very nature of his chosen field the pediatrician's world is largely populated by "little people."

Although there are those who would claim that the "little people" of today have changed greatly from those of past generations, we cannot feel that this is the case. Certainly the "Dennis the Menace[s]" of today had their prototypes in the past in the "Katzenjammer Kids" and "Peck's Bad Boy[s]" and others even more remote. Rather have the largest changes been made in the attitudes and viewpoints of the pediatricians themselves and more particularly in those whose help they have enlisted in the realm of child care.

References to the care of children may be found as far back as mankind has left any tangible evidence of his cultures and customs, but it is generally conceded that pediatries as a specialty had its inception little more than a century ago.

It was then that physicians first began to accept the concept that the "little people" of their world were not simply Lilliputian counterparts of their Brobdingnagian forebears—but actually a distinctly separate species concerned with totally different problems from their adult fellows.

As we review early pediatric history it is apparent that the physicians to children of that day and before—in accordance with the prevailing medical custom of the day—first leaned heavily upon the pathologist and his precursor the anatomist for assistance and concerned themselves primarily with the *diseases* of children. This was the era of Glisson, Sydenham, Cullen, Laennec, Stokes, Adams, and Cheyne, among others, and it is interesting to note that the emphasis upon disease engendered in this period was carried on for many years. Evidence of this may be found in a review of the titles of the early pediatric texts such as *Diseases of Children Still in the Cradle, A Treatise on Diseases of Children, De Morbus Puerorum, De Morbis Acutis Infantum,* etc. The earliest American pediatric texts are said to be Dewees' *The Maternal Physician: A Treatise on the Nurture and Management of Infants From Birth Until Two Years Old,* and Meigs' *Observations on Certain of the Diseases of Young Children,* among others.

Such widely known present-day textbooks as Holt's *Pediatrics* and Nelson's

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Pediatrics are direct descendants of the elder Holt's *Diseases of Children* and Griffith's similarly titled text.

It is of interest here to note also that among the earliest children's hospitals we find the famous Great Ormond Street Hospital for Sick Children in London (1852) and the Hospital for Sick Children in Toronto (1875).

A natural corollary of the emphasis on disease and physical diagnosis was that the pediatricians of this period became widely known as diagnosticians and frequently "doubled in brass" as the internists of the day. Here we recall Charles West, Sir Bence Jones, Sir William Jenner, Sir Archibald Garrod, among many.

The next step in pediatric history followed quite logically as attempts to control diseases led to a further study of their causes and a growing interest in *bacteriology* and, ultimately, its companion, *immunology*. Here we find such stalwarts as Jenner, Pasteur, Roux, Klebs, Loeffler, Schick, Ramon, Park, Calmette, all well remembered for their early contributions to microbiology and immunology.

With improved sanitation and a better understanding of such scourges as "cholera infantum" and "summer complaint," interest in infant feeding became greater. Here the *biochemists* made their first advances into the pediatricians' world and we can follow with interest the respective attention paid to fats, proteins, and carbohydrates as the offending elements of artificial formulae. For a brief period a "percentage" formula became popular, and it looked as if the mathematician would be the next important ally in the field—but the mere complexity of this method soon led to its death from disuse. Here we find our prototypes of that day known primarily as "baby doctors" with a special knowledge of infant feeding. Names such as Czerny, Kleinschmidt, Beidert, Finkelstein, and Heubner come to mind. The continued influence of the anatomist and pathologist can be found during this era in such names as Virchow, Neurath, Schüller. This was the age of heavy Germanic influence, and the biochemical viewpoint was carried over to this country by the many American pediatricians who received their early training under these men. Particularly significant in this regard is that Williams McKim Marriott was an instructor in biochemistry in 1914, and Professor of Pediatrics at Washington University three years later!

It can be seen, then, that at about the time that the two men whom we honor by this lectureship today were becoming established in pediatric practice, the pediatrician had drawn into his world not only the "little people" with whom he is working but also the anatomist, the pathologist, the microbiologists, and immunologists, and, more recently, the biochemists.

Through the combined efforts of this group, deaths from infectious diseases dropped remarkably and the concomitant study of growth and development and the detection and prevention of deficiency states brought about material changes in pediatric practice. About this time many "prophets of doom" stated publicly their fears that a pediatric specialty was doomed and that the field of the pediatrician was being so reduced by his own efforts that he would soon be putting himself out of business.

Next we came into the era of the *psychiatrist*. Here, for almost the first

time, the pediatricians were made conscious of the importance of their role in guiding the mental and emotional growth and development of their "little people" (and their parents) if they were to do their job in the total care of children. Dr. Frederick Allen, Dr. C. Anderson Aldrich, and others who pioneered in the development of child guidance clinics slowly but surely made their influence felt in the pediatric world, and it was a bare decade or so before the writings of Dr. Benjamin Spock became so generally accepted by the public that few pediatricians would have the temerity to practice without knowing what Dr. Spock says in *The Pocket Book of Baby and Child Care*. Arnold Gesell and his co-workers pioneered in the study of child development, and soon a number of pediatricians diverted a major portion of their interest into the realm of child guidance and child psychiatry. On the other hand, psychiatrists soon came to realize that adult psychiatry and pediatric psychiatry were not identical and that they, too, needed special training with "little people," if they were to enter into this challenging field. At the present time, then, we find a rather curious admixture of pediatricians turned child psychiatrists and child psychiatrists seeking pediatric knowledge and experience, working together toward a common goal. Only in the last few years can we say that the average pediatrician has accepted this group in his world and has become aware of the importance of this field of endeavor. That he did not do so sooner can probably be blamed on the slowness with which medical colleges in general accept new ideas in their teaching and the fact that only a few medical colleges, even up to the present date, have a carefully worked out, coordinated program between their departments of pediatrics and pediatric psychiatry.

Even more recently, and this brings me to my main theme for today, have pediatricians begun to be aware of the even wider scope of present-day pediatrics and the need for a greater understanding of many problems which up to this time have appeared to lie outside of their world.

PEDIATRIC ECOLOGY

This leads us to the present era, which I would like to call the era of social pediatrics. I know that to many people this term, of necessity, connotes socialized medicine with its well-known evils, and it is consequently looked upon with disfavor. Quite recently there has been a tendency to bring back an old term, that of ecology, which is defined as "the physiology of organisms and their environment" and we could, therefore, if we wished, call this the era of pediatric ecology, or one in which the pediatrician widens his world to include many things in the environment of his "little people" of which he has previously been largely unaware.

Parenthetically, it is rather interesting to note that this would seem to indicate somewhat of a completion of the cycle in that the pediatrician as a specialist is approaching more and more the ideal of the general practitioner of the older days, whose world encompassed all that pertained to his patients and not simply their diseases.

Why, you may ask, do I believe that this is of importance at this time? I can best answer this by reviewing a few of the conditions of which to me, it seems, we as pediatricians are in

many cases abysmally ignorant. By reviewing these conditions I hope to emphasize ways and means of meeting this need.

ACCIDENTS

First of all, I would like to call your attention to the fact that after the age of 2 years, accidents have become a leading cause of death among children.

Safety engineers and others in groups and organizations have been working long and hard to overcome the accident problem, but once again they need the help of the individual who first contacts the people who are the victims of these accidents. It is not by chance that the present movement toward the development of poison control centers was started by a group within the American Academy of Pediatrics and that this move is spreading very rapidly throughout the country. In many instances it has been taken over by the public health authorities, but the spark and stimulus has come largely from pediatricians. Home accidents and burns, as well as bicycle and pedestrian accidents, are mounting rapidly in the toll they take of young lives, and it behooves the pediatrician to study a bit more carefully what is being done in the prevention of accidents and poisoning and the proper care of these cases.

Probably the greatest single step possible in this field will not be taken until every pediatrician appoints himself as an accident-prevention committee of one to make as a part of every house visit a study of the problem existing in that home, and to review as a part of every well-child conference the accident problem with the mothers of today. All of us know that accidents tend to be found repeatedly in certain households and that certain children are definitely accident-prone. By discovering these and preventing their repetition, we can do far more in daily contacts with our little patients and their guardians than we can through all the literature and public pronouncements available.

ADOPTION

Next we come to the problems related to adoption. Despite the vast amount of work done in this field by social workers, public health and private welfare agencies, pediatricians in general have until recent years completely ignored the physician's role.

Whether, as is often the case, the physician plays a major role as the intermediary chiefly responsible for arranging the adoption, or whether his is the more minor role of furnishing medical care to one or another of the principals in this human drama, it is highly important that he be aware of the many ramifications of the problem and the numerous complications that may beset the ignorant and the unwary. It has frequently been emphasized that there is a threefold responsibility that must be met by all who deal with the adoption problem. The first is said to be to the child, the second to the natural parent or parents, and the third to the adopting parents. I would suggest that we add a fourth, that is, to the community, for it is the community which suffers most in cases of unsuccessful adoption. The immensity of the problem may be better grasped if we realize that figures from the United States Children's Bureau tell us that there were approximately 93,000 adoptions in the United States and its territories in 1955 as compared with a figure of about 50,000 eleven

years earlier in 1944. Comparable birth rate figures for these two periods would be 230 per 1,000 females in 1955 and 150 per 1,000 females for 1944, indicating that the number of adoptions has increased out of proportion to the increase in birth rate. Since approximately one-half of these adoptions result from placement with relatives of the natural mother and represent no special problem, we are concerned primarily with the remaining half, in which the children are adopted by unrelated petitioners. Of these it is interesting to note that nearly three-fourths of these children were born out of wedlock, either to an unmarried woman or to a married woman. Of the remaining children, about 4 per cent were children who had lost one or both parents through death. Further subdividing the group of the children adopted by unrelated petitioners, we find that 56 per cent were placed by public or voluntary social agencies; of the remaining 44 per cent, approximately half were placed by the parents or relatives and the other half independently by other persons. It is this latter group which causes so much concern, for here we find the "gray market" and the "black market" in adoptions.

But how, you may ask, are we as physicians primarily concerned with this? First, in considering our responsibility to the child, it is obvious that those of us who are concerned with the placing of children for adoption must make certain that the adoptive home will provide the child with all of the opportunities that might have been lacking had he remained with his natural parents. It is necessary to review carefully all the facts known about the natural parents as well as about the adoptive parents before we can be certain that this responsibility is adequately fulfilled. Even with the best intentions on the part of all parties involved, it is possible for one who is ignorant of the details of the law to fail to provide the necessary safeguards. At some later date, after the adoption petition has been filed for final action, the natural parents may change their minds and bring about a great deal of anguish for all concerned if a proper relinquishment has not been received. A child may be placed with a family moving to another state, and they, upon reaching this state, may find that they are unable legally to complete the adoption since certain requirements of the law there have not been fulfilled. It is also possible that the adoptive parents may change their minds and, if the natural mother has removed herself from the picture, the physician who served as intermediary may find himself responsible for the future care of the child.

Inasmuch as adoptive parents are, by the very nature of the step they take, extremely anxious to do all in their power to ensure the best possible care of their adopted child, in the majority of instances pediatricians are frequently called upon to give them advice and guidance. These visits provide many opportunities for the physician not only to guide the physical health and welfare of the child but also to assist the parents in bringing about a healthy and happy relationship with their child. Of particular importance in this regard is the fact that the child should be told at as early an age as possible that he is adopted and that in all truth he is a "chosen child," a truly fortunate situation! All too often parents are

prone to keep this information hidden from the child, only to have it crop up at some later date, with disastrous consequences. The pediatrician can help both the parents and the child immeasurably by showing them how much better it is for the mental health of all concerned to have this hurdle cleared as early as possible.

In the protection of the natural parents, it is obviously important to keep the mother from "a hurried decision to give up the child made under strain and anxiety." Since the physician is very often the first person to whom the unwed mother turns for help, it is his responsibility to see not only that the best possible medical care is provided for her but that the decision she reaches is one with which she may live comfortably for the rest of her life. The physician, then, must be in a position to see to the protection of her moral as well as her legal rights.

In regard to the responsibility to the adopting parents, we find that the pediatrician very often is requested to examine the child and decide for them whether or not the child is fit for adoption. All of us know how very difficult it is to prophesy the future of a young infant, and we cannot be too careful in our examination. Frequently the pediatrician is handicapped by a lack of knowledge of the background of the child in question, and overanxious adoptive parents may at the moment be inclined to accept responsibility and, later, should a congenital defect present itself, try to "return" the child because of the unforeseen complication. It must be carefully explained to all adoptive parents that although every possible safeguard has been given them in the light of present knowledge, there is still a faint possibility, which could be true of a child of their own, that some handicapping condition may subsequently show itself and that they should meet this situation as they would if the child had been born naturally to them. It is comforting to note that in recent years more and more adoptive parents have taken handicapped children with full awareness of the existing handicap and have helped them to develop into fine young people through their loving care and affection.

One of the questions that is being put to physicians constantly concerns the age at which a child should be adopted. I have yet to find a definitive answer to this question. Most of us agree that the earlier the child and the adoptive mother can be brought together, the better the chances are for a completely satisfactory psychologic adjustment, and this advantage must be weighed against the disadvantage of a relative inability to foresee problems when the child is examined at a very early age.

Although pediatricians are less concerned directly with the care of the unwed mother, it is interesting to note that in a survey recently conducted in New York City, it was found that 47 per cent of the unmarried mothers had received no prenatal care as compared with 4 per cent of a similar series of married mothers. Along with this we find a much higher percentage of nonhospital deliveries among the unmarried women and consequently a much higher mortality rate and certainly a much greater perinatal mortality. With this we are necessarily concerned, and it is the direct responsibility of the medical profession to see to it that the best possible care is given both the mother and the child, regardless of

complicating social and economic circumstances.

Another important field for the physician is that of advice to adoptive parents. Not only should he inquire carefully into the motivation for adoption prompting these people, lest they be led into a false move in an effort, for example, to replace a child of their own who has died by one who is adopted, when they are unable emotionally to accept this change, or when, as is often the case, an adoption is looked upon as a possible cure for marital difficulties of long standing. Even those who have the most sincere motives may be emotionally or otherwise incapable of giving a child the proper opportunities. Here the responsibility lies with the physician to help them make the proper decision.

For all these reasons it seems obvious that although many successful adoptions have been made independently through the advice of a physician who knows the adoptive parents quite well and who knows of a mother who wishes to place her child out for adoption, the chances for a successful adoption are enhanced if the services of an experienced social agency are brought into play.

It is quite important that the physician be well acquainted with the adoption laws of his particular state. He must know whether or not his state permits relinquishment of the rights of the mother to individuals or to agencies and whether or not a particular infant is adoptable by reason of abandonment. He must know whether the particular state in which he practices has a law forbidding the adoption of children by parents of a different religion or race. He must inquire carefully into the law regarding interstate adoptions.

To solve such problems we must, then, include in our pediatric ecology a group of social scientists which would include necessarily the lawyer, the social worker, and frequently the psychologist. All these, also, must be brought into the pediatrician's world. That we are in many cases not yet ready for this is amply shown by the attitude of many practicing physicians to social workers and welfare agencies in general. In such cases, closer relations and a better understanding are the keynote toward cooperation.

SCHOOL HEALTH

Next in the realm of pediatric ecology, or social pediatrics if you will, I would like to mention the school health program. I am prompted to do this by the interesting fact that in the state of Pennsylvania in a recent year less than 3 per cent of school health examinations were done privately in a physician's office. This is particularly strange in view of the fact that for the country as a whole the American Medical Association states that more than 50 per cent of such examinations are done by private physicians and that, in certain areas, as, for example, one urban area in Wisconsin, through a concerted effort to have children examined in physicians' offices, examinations by school physicians were decreased from 3,200 in one year to 71 three years later. Another interesting contrast is that in Evanston, Illinois, "A committee of the Medical Society worked with the schools for the end that 90 per cent of the children were examined by their own family physicians," whereas in Philadelphia in 1955-1956, of 77,300 pupils examined,

only 1.46 per cent were examined by private physicians. It is scant consolation indeed to note that the dentists fared even worse, for the percentage of dental examinations done privately in the same year was 0.3 per cent!

Why is this so? There are many reasons, but I believe a major one is the lack of understanding on the part of all physicians as to the true scope of the school health program.

The total school health program is said to consist of three main fields. The first of these might be called school health services. These in turn may be defined as any of the following procedures which are established: (a) the appraisal of the health status of pupils and school personnel; (b) the counseling of pupils, parents, and others concerning appraisal findings; (c) the encouraging of the correction of remedial defects; (d) the assisting in the identification and education of handicapped children; (e) helping to prevent and control disease; and (f) the provision of emergency service for injury or sudden illness.

Second under the school health program comes school health education, which may be defined as the process of providing learning experiences for the purpose of influencing knowledge, attitudes, or conduct, relating to individual or community health.

Third, we have healthful school living, which designates the provision of a safe and healthy environment, the organization of a healthful school day, and the establishment of interpersonal relationships favorable to emotional, social, and physical health. Analyzing these, we note that the school health appraisal or examination is a very minor part of the whole school health program and that, properly viewed, the school health program fits ideally into a pediatrician's program for the care of his "little people." No one will gainsay the fact that the physician who has been periodically examining a child is the one best equipped to appraise his status at any one time, and every effort should be made to see to it that school health examinations as such are done by him with the complete cooperation of the school health authorities. Not only should he have a full record of the child's medical past but he should be fully appraised of any problems which the child is presenting in school so that he may aid in their correction and interpretation. Furthermore, those involved in the school health program itself must be encouraged to take the broader view that these examinations are a very small part of their job and that the education of the parents on the value of these examinations and the need for follow-up through proper sources is quite important, as well as the opportunity of giving good health education to the parents and child alike. The insurance of a healthy environment, the prevention of contagious disease, the care and supervision of school athletics are other phases of the program which time does not permit us to discuss in any detail but which are obvious to anyone who carefully studies this problem. All in all, then, there seems to be much left to be done by all of us in insuring our "little people" the best kind of school health program.

HANDICAPPED CHILDREN

Next on my list under social pediatrics I would consider the care of the handicapped child. It has only been in recent years that efforts have been

made to coordinate the many individual groups who are working hard to bring about the best possible future for handicapped children. Dr. Wishik has pointed out that one out of every ten children in the United States has one or another handicap which interferes with his normal emotional, intellectual, or physical growth and development. He further noted, "One-third of these children have a single handicap only, a second third have two handicaps, and the remaining third multiple handicaps."

At a recent Pennsylvania State Conference on the problems of the handicapped child, Dr. A. R. Shands, Jr., Medical Director of the Alfred I. Dupont Institute of the Nemours Foundation, a group which has sponsored a number of state-wide meetings looking forward to the establishment of community programs, brought the interesting thought that the problem of community needs for the child with a handicap can be summarized under the five "E's."

These five "E's," he suggests, are (1) enumeration; (2) evaluation; (3) education; (4) eradication; and (5) emancipation.

Considering the physician's role in each of these it is obvious that if we are to have a reasonable survey of how serious the problem is in each community, the physician, and the physician alone, is able to bring about a true analysis of the local problem.

As to the question of "evaluation," this, of course, means adequate diagnosis and complete planning for total care. Here again the family physician must not only serve as a leader of the team but must be fully aware of all of the resources available in his community and ways and means of securing them for his patients.

Next, under "education," all of us are aware of the problems brought about by a handicapped child in a family. Not only must the child be educated properly to live with his or her handicap, but the parents must be given a great deal of help in learning how they can best meet the problem from their own viewpoint and from that of the child, his siblings, and the community in general. Finally, the community must be educated to the fact that these handicaps should not be hidden away but should be brought to the surface and treated just as any other illness would be handled. All of us who visited the Selinsgrove Colony last month received a very excellent lesson in the education both of the children and of the community in the proper attitude toward children with different kinds of handicaps. Such problems as whether or not a severely handicapped child could be best cared for in his own home or in an institution can only be answered through the help and guidance of the physician who best knows the child and the family. All of us realize the necessity of keeping the child in his own natural environment in so far as it is possible. We realize that it is only if and when the child's presence in the home creates further problems in the family itself or when remaining in the home makes it impossible for the child to receive such benefits in the way of instruction and training that he needs that institutionalization is considered advisable. Parenthetically we might add, also, that the medical profession itself needs a great deal of education into a better understanding of handicapped children and their problems.

Eradication means the prevention of handicaps wherever possible and their treatment after their development. This in itself is a broad field, and once again the family pediatrician is the key man.

The final "E" was that of emancipation, or transference from dependence to independence. In order to achieve this we must apply the preceding four "E's" to the fullest extent. Here indeed is a broad field open to all of us, in which few can pose as experts today.

JUVENILE DELINQUENCY

The final problem which I would like to bring to your attention as belonging to pediatric ecology is one of the problems of adolescence, familiarly known as "juvenile delinquency." A great deal has been written but little is known about this most important subject. In presenting this discussion I would like to start with the following quotation. "Is the behavior of children becoming increasingly shocking? Confronted with the worrisome problem of juvenile delinquency one lone writer summed up the situation in his vicinity in these blunt words: 'Our youth now love luxury. They have bad manners, contempt for authority, disrespect for older people. Children nowadays are tyrants. They no longer rise when their elders enter the room. They contradict their parents, chatter before company, gobble their food, and tyrannize their teachers.'" Of interest is the fact that this is not a quotation from a recent writer, but these are the words of Socrates, written in the fifth century before Christ.

It is obvious, then, that the problem of juvenile delinquency is not new, but is as old as any of the problems of our children. My work on the Governor's Committee on Children and Youth has impressed me with the fact that a very small percentage of physicians show any interest at all in this problem. It has only been in the last year that the American Academy of Pediatrics established a Committee on Juvenile Delinquency, and before that only a few states had started active programs. Here again we have an example of a physician whose world is too small, who needs to enlarge it if he is going to do a complete job.

How, you may ask, can he accomplish this in this field? Juvenile delinquency has been defined by Bertram Beck as "a pathology transmitted by the community to the family and thence to the individual." A review of this definition indicates that we must have a community at fault, then a family at fault, and finally a receptive individual. It is with the latter that I believe the pediatrician can be of the greatest help.

To understand the problems of juvenile delinquency, it seems to me that it is necessary, first of all, to understand the problems of the adolescent. All of us are aware of the fact that for many years adolescence has been a medical "no-man's land." Too frequently the children who have been under our pediatric care for the first ten or twelve years of their lives no longer are seen by us and still have not fallen under the care of our successors, the internists. The reasons for this, of course, are multiple. One of the reasons lies in the fact that too many of these children become self-conscious in the pediatrician's office and fight shy of the "baby doctor." It is their own choice that they no longer come to the pediatrician. Many of them would

really like to, but cannot stand the apparent implication that they are not growing up. Proper handling and the setting aside of special office hours for such patients might well solve this phase of the problem.

A second cause lies with the parents. Since these children have gotten through the period of acute contagious diseases, and since they have comparatively few physical illnesses, it is rather normal for the parents to feel that they no longer require regular and routine medical supervision. Here, of course, we must admit that had they been properly educated by the pediatrician in earlier years, this problem might not exist. Nonetheless it does, and it is important that we make them realize that the rapid growth period associated with adolescence has many problems peculiar to itself that need specialized medical care. Thanks to the pioneering work of Dr. Roswell Gallagher and others, pediatricians are beginning to become aware of the need for the medical supervision of adolescents and are extending their field to include, rightfully, I believe, this phase of life.

Pediatricians in general, however, have not yet caught up with this, nor are they acquainted with the physical and psychological problems of adolescence to the extent that they must be if they are to meet this problem successfully.

Not only do we have the problems of rapid growth, those of the deficiency states, endocrine disorders, osseous abnormalities, and others, which are seen so frequently in this age period, but we also have the normal psychological problems which the average adolescent must face. When we realize that the normal adolescent in the process of growing up must meet four major problems successfully if he is to grow into a well-adjusted adult, we can get some insight into the reason that so many of them fail to do this. These have been defined as (1) the newly developed and increasingly active sex instinct, (2) the normal battle between their newly developed sense of independence and their older state of dependence, (3) their normal heterosexual development, and (4) a normal feeling of inferiority and inadequacy.

Those who have studied the matter carefully point out that several things must be done to aid the adolescent to meet these four problems. First of all, the adolescent must be encouraged to do something well; this gives self-confidence, regardless of the particular field of endeavor. Second, every adolescent must be made to feel that there is a place for him or her in society. Since society starts in the home, the home must give these young people a conscious and active place before the community will do likewise.

When these conditions are not met, and particularly when the adolescent is handicapped by illness, by family breakdown, or by severe economic and social stress, it can be readily seen why many of them get into difficulty with society.

Measures to prevent juvenile delinquency have been summarized in three categories. The first of these is the promotion of normal, healthy personality development in all children. Certainly this is an integral and active part of pediatrics, even though often neglected. The second is the reaching of a potentially delinquent child before he gets into trouble. Here, again, the pediatrician is often the first to realize that this particular child, who is a

school problem, a social problem, and possibly has psychosomatic symptoms, is the one who needs help. If he has the time, the knowledge, and the experience, he will give this help. If he does not, it is his duty to see that the child receives it elsewhere. The third measure, that of reducing the tendency toward more repeated offenses, falls more in the realm of the welfare agencies and the local and state authorities. Unfortunately, human society is such that we tend to punish those who do not do as we think they should in an effort to excuse our own lack. Consequently, we find much greater emphasis on bigger and better detention homes, curfew laws, more parole officers, conservation camps, etc., than on the first two aspects of our problem.

In addition to these preventive measures, juvenile delinquency can be helped, first, through a therapeutic and educational program, second, through measures aimed at improving the environment, third through the early detection of potential delinquents, and, finally through an understanding of the normal adolescent and his or her problems.

It is interesting to note that studies have shown that it is not the economic status of the community, the presence or absence of minority groups or racial mixtures, the number of social agencies, Boy Scout troops, boys' clubs, and other organizations in the community that determine whether or not juvenile delinquency will be widespread in that particular area. The important factor seems to be the presence or absence of a community spirit of cohesiveness. Where the population is relatively stable and where a spirit of neighborliness and of common goals and common interests has developed, juvenile delinquency has diminished. Conversely, where the population changes rapidly and where people have little or no knowledge of their neighbors and have little or no common interests, juvenile delinquency is found to be rampant.

Careful studies have also shown that the potential delinquent can often be foretold by a careful study of the relationship between the parents and the children, and certainly no one is better equipped to know the situation in the individual home than the family pediatrician. It is for this reason that I feel that we as physicians to our "little people" owe them an understanding of their problems and must accept the responsibility for a leading role in their correction.

CONCLUSION

What solution, then, can we offer the pediatrician in his new changing world? We have shown that the pediatrician very early took the anatomist and the pathologist into his world. Shortly thereafter he added the physiologist and the biochemist, and, still later, the psychiatrist and the psychologist. Now, it seems to me, we must open up our world to include the specialists in the social sciences, the social worker, the welfare agency, and the local and state groups dealing with children. To do this satisfactorily we must have, first, an improvement in our medical school teaching. Few of us have had courses on any of these topics. It is interesting to note that only one of the standard pediatric textbooks bears any reference to adoption, and, as far as I have been able to find, none deals with juvenile delinquency. Only occasionally does one find such authors as Dr. Harry Bakwin writing on these topics in our current pediatric journals.

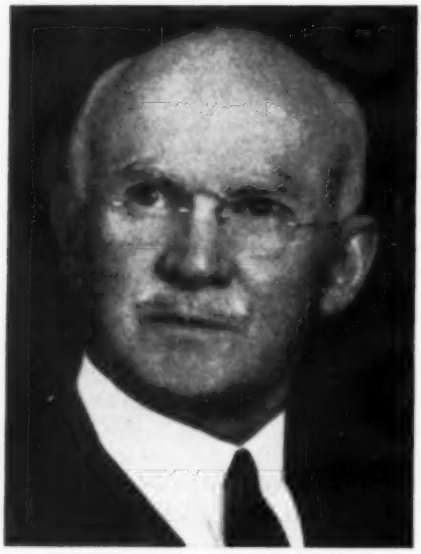
In addition, we must educate the physician already in practice, both the general practitioner and the pediatrician, to the needs here outlined and the ways of meeting these needs. This can be done primarily through medical meetings like ours here today and through our publications. Next, we must encourage our local, state, and national societies, both general and specialty, to add more discussion of these problems to their programs. I am glad to say that this is being done.

Finally, we as individuals must take it upon ourselves to take an active role in our community's efforts to correct these problems. We must not be content to serve merely as advisors, but, in so far as it lies within our power, we must take active roles of leadership in all of these many aspects of child care. Then and only then, can we say that we are truly making the most of our new world with the optimum results for the "little people" under our care.

Pediatric Profiles

Samuel McClintock Hamill

(1864-1948)



PROBABLY no man in the field of pediatrics without high academic title ever attained such stature or was accorded such honors and distinction as Sam Hamill. An academic title in his case was not a requisite for attaining stature, for holding the warm affection of his younger associates who had such academic standing, or for elevating him to some of the highest positions in his professional fields of interest.

Not only was he a distinguished American, as distinguished as we have had in this field, but he fully played and looked the part; a man suave, with elegant manners, but still warmly personal to his friends; immaculately and distinctively groomed, with a slender erect frame, and yet fully able to unbend with younger associates, so many of whom deeply enjoyed his company.

To picture him as most of his associates remember him, so often throughout most of his life, was to see him at the table in a conference, in a committee meeting, or at a board meeting. Because he had accepted with graciousness many administrative obligations, there were few who attended so many meetings of this general nature as he did. He more often than not sat at the head of the table, a sharp twinkle in his deep-set blue eyes which never wavered from the pursuit of the business at hand, a brilliantly ruddy complexion with red apple sheen on cheeks and bald pate.

As Punch parodied in "The Night After Christmas," "His eyes how they twinkled, had the doctor got merry, his lips looked like port, and his breath smelled like sherry." At the evening meetings he could well have out-punched Punch's description. Carefully trimmed hair, which grew to be snow white quite early, edged his shining pate, and his full port-wine lips under a carefully clipped white

moustache firmly held a cigarette holder into which from time to time he fitted a cigarette with the most meticulous precision. A white jet stream of smoke, as if to emphasize the firmness of decision, mushroomed abruptly straight upward, past his nose and then, like the four winds, blew first to one side, then the other, all in a single swirl of decision, with a clear crisp statement at the end. His speech was always carefully and precisely prepared and delivered. His attire included a handkerchief well arranged in the left pocket, an immaculate tie, shirt, and suit, the last being frequently dark with a pin stripe, alternating in the summer with flannels or a linen suit and shoes all of spotless white. The care of attire and the precision of handling meetings were important things in his life—they represented a natural rightness of approach and mastery of environment which sketched in the boundaries of conduct he had set for himself. To an important extent his expectations of himself and many of the rules by which he lived came into a certain osmotic equilibrium with those who associated with him; at least the younger men in his presence felt the stimulus of such standards, nobly laid down and brilliantly exemplified. And he in turn gained much from them.

In precisely the same way that he set the highest standards for himself he also set them for those with whom he worked and for the younger men around him. He abhorred carelessness of dress or behavior at such times as dress and behavior seemed to him important parts of the setting, but he could equally well relax and enjoy golf or an evening's pleasure, fully participating with his associates. Even then there remained an aura of dignity in speech and action—he could not have been boisterous but neither could he make others feel restrained in sports or pleasure.

In his younger days his high standards together with his keen commanding presence made him appear cocky and too self-assured to many men who did not know him well. This appearance was greatly accentuated at times by his jumping actively into the forefront of all sorts of medical issues. The social obligations he felt so deeply for children extended broadly into affairs of administration in the medical school of the University of Pennsylvania. He attended Princeton University and graduated from the School of Medicine, University of Pennsylvania (1888), and after internship, ending in 1891, he started general practice in central Philadelphia, finally restricting his work to pediatrics in 1901.

An experience in Escherich's clinic in Vienna in 1905 gave him a splendid insight into the development of the experimental method in the pediatric field. This glimpse into European science and what academic medicine could achieve when firmly founded upon the research methods of Claude Bernard and the cytopathology of Virchow placed him in the forefront of those at the University of Pennsylvania who recognized the then existing handicaps of descriptive medicine, represented for want of greater knowledge and broader perspective, by James Tyson, professor of medicine, and a number of his associates.

Hamill in these early years was looked upon as a "firebrand" and appeared always to be in some sort of fracas. In justice to him, these

controversies were usually the result of his clear objectives to improve the health of children or the value of medical education and medical science.

When David Edsall was asked to leave Pennsylvania to head the medical school at Washington University, Hamill organized and became chairman of a committee of the medical alumni which was chiefly responsible for Tyson's resignation from the chair of medicine and the elevation of Edsall. Hamill was a "devil" or "angel," depending upon which camp one belonged to—at that time it was impossible for anyone to be neutral about him.

Edsall's appointment aroused enthusiastic hopes among younger men on the University of Pennsylvania faculty and especially among the new appointees who came to Pennsylvania on his recommendation, that clinical investigation and its relationship with the preclinical sciences would be fostered to a degree which had not hitherto been the case. His resignation only a few months after his appointment provided a setback, recovery from which did not occur for several years.

Hamill's own influence within the medical school was never again felt as an important force; nor was he accorded a rank which, because of his knowledge, influence on young men, and capabilities for teaching, he fully deserved.

Also in 1910 by an unfortunate coincidence, he became embroiled in a public controversy arising from the very type of clinical investigation he sought most to stimulate. Kenneth Blackfan had not found what he greatly desired in general practice at Cambridge, New York, and after returning to Harry Shaw at Albany decided to obtain additional experience with Sam Hamill. From this happy coincidence arose a fast and lifelong friendship between Hamill and Blackfan despite a difference of 20 years in their ages. Nonetheless this firm relation was born, "untimely ripped" from the womb, in newspaper publicity concerning work they were conducting at the St. Vincent's Foundling Hospital where Blackfan had been appointed as resident under Dr. Hamill. The fact that the hospital was reliably known to have at that time a mortality rate of about 90 per cent for infants under 1 year made it a fertile field for clinical investigators, and particularly for one who had the crusading and, at times, the castigating nature of Sam Hamill. The sisters soon felt a sword of Damocles poised above them and laid about them for any bludgeon that might destroy the searing evidence Hamill and Blackfan were accumulating against their care of the infants. This they found in the clinical research being conducted by Hamill and Blackfan on the von Pirquet skin test and the Calmette eye test for tuberculosis. The eager suspicion of the sisters was soon rewarded by their observing the mild conjunctival reaction produced by the Calmette eye test, and the trap was sprung when the newspapers, carefully posted by the nurses, broke into daily headlines concerning the use of the infants as "guinea pigs" to satisfy alleged sadistic tendencies of the two scientists "with hearts of stone." Whatever else might have been said concerning them during the course of their lives, where infants were concerned, they were "softies." To be thus falsely and maliciously pilloried in the public press was trouble enough, but to have all

future studies destroyed in an institution ideally suited for investigations under controlled conditions placed a pall over pediatric research in Philadelphia of which one is still reminded even to the present time. Hamill's opportunities, which had been few enough in academic institutions, were practically ruined, and Blackfan shortly thereafter went to St. Louis and to Johns Hopkins with John Howland for more fertile fields of pediatric research.

Hamill joined with Charles Fife in 1911 in the redevelopment of a summer department of the Children's Hospital at the edge of Fairmount Park for the care of summer diarrhea. This department had been closed for several years by the board of managers of the Children's Hospital, and Fife asked Hamill whether he would help in its re-establishment. Kenneth Blackfan and Borden Veeder became residents there. Since the Children's Hospital had no accommodations for infants (0 to 2 years), Drs. Fife and Hamill soon developed the idea of a babies' hospital to care for this age range, particularly on an outpatient basis, with a small number of beds. With their support this was soon built at 7th and Delancey Streets. The Philadelphia Child Health Society was another outcome of their joint effort and Hamill was president of this for many years. Quite appropriately this society was laid down when the Babies Hospital was developed into a demonstration health center for Philadelphia as the Fife-Hamill Health Center, thus perpetuating the joint efforts of these two pediatric pioneers and close friends.

During World War I, Hamill was Chairman of the National Child Welfare Committee, Council of National Defense, Member of the Medical Board of this Council, and Director of Child Welfare for the Council of National Defense. He was a delegate to the medical conference of Red Cross societies in Cannes, France. After forty years of active practice he "retired" in 1929 to devote his time and energies to all children.

The work and leadership of Dr. Hamill in the Third White House Conference, called by President Hoover in 1930, was the high point in his medical career. There were four general sections, and Hamill was chairman of "Section I, Medical Service," with Van Ingen and Blackfan serving as vice-chairmen. They divided the field into 3 main groups: "Growth and Development" with the committee functioning as a whole under Blackfan; "Medical Care" under the general supervision of Van Ingen with 13 subcommittees; and "Prenatal and Maternal Care" under Fred Adair with 6 subcommittees. All filtered back to Hamill for guidance and decisions. President Hoover, who like Hamill, had been President of the American Child Health Association, was greatly interested in child health, and ample funds were made available. Some of the Committee worked for over a year on the preparation of their reports, which were published in a number of volumes in 1931. The two-volume report by Blackfan's committee on "Growth and Development" became the standard text on the subject and the vade mecum for many years for younger pediatricians preparing to take the Pediatric Board examination for certification. The work of the Section on Medical Service under his stimulating leadership so far surpassed that of the other three sections that the "Third" among the five White House Confer-

ences has gone down in history as the "Health Conference."

When the conference was over, the problem arose, as always, of implementing the findings and the carrying out of the recommendations. Not content to rest on what he had accomplished in a broad way for the health of all of the children of the Nation, he took upon himself for the remainder of his life the responsibility for putting the recommendations into effect in his own state, Pennsylvania. In this he turned again to the younger pediatricians in Philadelphia and throughout the state.

One of his close pediatric friends, a man some 20 years younger, once asked him his secret for staying so young in thought and actions. He replied that many years before, when he was a youngster breaking into pediatrics, the doorbell rang at his home on Spruce Street one day and Dr. Jacobi was ushered in. He said that he was not only flattered but quite flustered that a pediatrician of Dr. Jacobi's standing, some 34 years older than he, had come to make a friendly call. This was the beginning of a friendship between the two men. He (Hamill) once asked the same question of Jacobi, who replied it was due to his keeping close friendships with younger men as well as with his contemporaries. "This implied advice," said Hamill, "I took to heart and have tried to follow."

When Graeme Mitchell left Philadelphia for Cincinnati, an unfortunate hiatus became apparent between the "elder statesmen" in Philadelphia pediatrics and men or women still in their early pediatric training. Few or none remained to follow the footsteps of Hamill, Gittings, Griffith, Carpenter, Hand, and Fife. In addition, none of these elder statesmen had entered the full-time clinical field.

Since he had early learned from Jacobi the mutual value of staying close to young men, in his later years, even in the absence of academic connections, Hamill became a rallying point from which the development of young men and women interested in the broader aspects of pediatrics was guided. The work of the Philadelphia Child Health Society also gave these efforts added impetus. Many of the next generation of pediatricians have remembered the pleasure and profit of long evening meetings at his home, where the medical and the social were combined with notable graciousness—in this he had few who equaled and none who excelled him.

In the relatively short history of pediatrics Sam Hamill stands in a unique niche—a man whose personality and stature required no academic forum—a man whose imprint on the field of child health, through the White House Conference and its emphasis on the promotion of health, will extend from generation to generation and "to their children's children."

Joseph Stokes, Jr.

Comments on Current Literature

RECENT DEVELOPMENTS IN THE STUDY OF MEASLES VIRUS

ATTEMPTS to study the etiologic agent of rubeola experimentally began as early as 1759.[1] Through the years successful results were obtained transiently, but the agent was difficult to transfer to hosts other than man, and apparently was difficult to maintain. By the early 1900's, monkeys were known to be susceptible, the clinical disease having been transmitted successfully to several species of Macacus.[2] The filtrable nature of the agent was recognized early. Plotz,[3] in the 1930's, then at the Pasteur Institute in Paris, was perhaps the first to employ the embryonated hen's egg and chick embryonic tissue. Somewhat later (1939-1941) Rake, Shaffer, and their associates[4] first reported the series of experiments which involved cultivation of measles virus in the fertile hen's egg, reduction of its infectivity by multiple egg passage, and on subsequent transfer to monkeys, the occurrence of mild but typical clinical disease, with the projected possibility of developing a vaccine. However, the virus was difficult to maintain, the procedure expensive, and the induction of clinical disease in monkeys not possible with consistent regularity. As Dr. Enders, interested in this disease for many years, has pointed out, "a convenient and inexpensive technic whereby virus multiplication could be unequivocally determined"[5] had not yet been perfected.

In 1954 Enders and Peebles[5] were successful in isolating a viral agent from whole blood and throat washings obtained during the first 24 hours of the exanthem from a patient with typical clinical manifestations of measles. Human embryonic kidney tissue growing in roller tube cultures was exposed to both whole blood and throat washings. After an interval of from four to ten days, cytopathogenic changes became marked, with the formation of large multinucleated giant cells, the nuclei of which contained eosinophilic inclusion bodies. In seven other typical cases of measles, blood and throat washings yielded immunologically identical cytopathogenic agents. In addition, an agent indistinguishable from the other strains was recovered by means of tissue culture from the lung of a patient who died during the acute stage of measles. These nine strains of measles virus were isolated from patients resident in different geographic localities at two distinct times, in the spring of 1954 and of 1955. Subsequently the virus of measles was recovered with comparative ease from patients in early clinical phase, and has been propagated by a number of investigators in several different types of human and monkey tissue, and in cultures of human cancer cells.[6]

The Enders group of investigators (Dr. Enders and his present associates) has published recently three reports which are concerned with the isolation and cultivation of the measles virus, the nature of its infectivity for monkeys, and the spontaneous occurrence in monkeys of a disease similar to measles, the etiologic agent of which is closely related antigenically to that of measles. The first of these reports, that dealing with the experimental infection in monkeys and the occurrence of spontaneous "measles" infection among monkeys, appeared in January, 1957, in the *Journal of Immunology*.[7]

This investigation was undertaken primarily in order to ascertain "whether virus isolated from patients with measles, and propagated in tissue cultures, is capable of reproducing in monkeys the essential features of the human disease."[7] It was shown that inoculation of selected cynomolgus monkeys with material from the twenty-third virus passage, as well as virus inoculum from first or second tissue culture passages, resulted in infection and clinical manifestations basically comparable to the clinical disease in man. The incubation period appeared to be about ten days, followed by an exanthem of four to five days' duration; a moderate leukopenia began about the seventh day following inoculation and lasted for from two to five days. Viremia, apparent about the fifth day, was present for from two to five days. Complement-fixing and neutralizing antibodies were detectable shortly after the disappearance of the rash. These findings were definite and fairly easy to evaluate. Not all monkeys, however, developed an exanthem, and one developed neither rash nor viremia. All did respond antigenically by increase in antibody titer.

In selecting monkeys for use in the experimental study, a certain proportion of the animals was found to have already appreciable titers of complement-fixing and neutralizing antibodies to the cultured strains of measles virus. Such antibodies are known to be present in the blood of a large majority of rhesus monkeys held in captivity for a period of time. In the present series such antibodies could not be demonstrated in 31 cynomolgus monkeys tested shortly after capture. In five cynomolgus monkeys spontaneous infection occurred which was similar to that following experimental inoculation, and all five developed increasing titer of antibodies to the cultured strain of virus. These findings are discussed by the authors in some detail, since they may be of considerable significance. In a laboratory colony of monkeys spread by close association, contact, or human carrier such as an animal attendant would seem to be the simplest explanation. It is well known, however, that the rhesus monkeys commonly used for experimental purposes are collected in India from forest areas near thickly populated sections, and that many show antibodies to human disease agents. In transit cynomolgus and rhesus monkeys may be in relatively close proximity.[6] More important, however, as the authors emphasize, is the possible spontaneous occurrence in monkey populations of a simian strain of virus, antigenically indistinguishable from the human measles strains, which is epizootic or enzootic among monkeys. Such a question is of ". . . intrinsic biologic interest to those concerned with . . . the interrelationship between human and animal diseases."[7] Furthermore, should the simian agent "prove to have a separate existence, it might exhibit lower pathogenicity for man than the human strain,"[7] and after the manner of the vaccinia-variola relationship might prove of value for immunization purposes.

Two other reports by this group of investigators[8] appeared in March and in May, 1957, and together comprise a careful summary of experimental results concerned with the isolation, propagation, properties and behavior of strains of measles virus with emphasis on the cytopathogenesis in various types of tissue culture, in human amnion cells, chick embryonic tissue and in the developing chick embryo. From the standpoint of the cytopathogenesis, certain features are of interest: not only the occurrence of syncytial multinucleate giant cells showing intranuclear and intracytoplasmic inclusion bodies,[5] but the identification of a newly recognized type of cytopathogenic change in tissue cultures inoculated with measles virus: ". . . the assumption by individual epithelial cells of a characteristic fusiform or stellate configuration."[8] Some of these affected epithelial cells showed eosinophilic intranuclear inclusions resembling those observed in the nuclei of the syncytia. Both types of cytopathogenic change led to cellular necrosis and disintegration. In human

amnion cell cultures, both types of pathogenic change were observed, while in cultures of kidney cells infected with measles virus, only the syncytial multinucleate type was observed.

During the course of these experiments a strain of measles virus (the Edmonston strain) was maintained in embryonated eggs for at least twelve successive passages. Presence of the virus, which is not apparent on examination of the embryonated egg, was demonstrated at intervals by transfer to amnion cell cultures, and the virus was identified at intervals as the original strain by appropriate complement-fixation and virus-neutralization tests.

In considering the possible use of the egg-adapted measles virus as an antigenic material for human immunization purposes, the authors emphasize that much remains to be done, but that important ground work has been laid, and that "attempts to immunize man against measles with egg-adapted virus can again be undertaken under more precise conditions of control than were available to workers in the past."[8]

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I have been following the literature on aminophylline poisoning and I am somewhat disturbed by the conclusions reached in the editorial of the June, 1957, issue stating that "The dosage schedule for aminophylline. . . is safe and probably usually adequate."

My personal experience is as follows: In 1948 I prescribed ¼ of a suppository t.i.d. for a 20-month-old girl, a dose then considered quite conservative. Shortly after the first (and only) dose the child developed vomiting and severe tonic and clonic convulsions. These seizures subsided after intravenous Pentothal and the girl eventually made a complete recovery though she suffered a temporary postconvulsive hemiplegia. Within the next year two additional cases of aminophylline poisoning from rectal suppositories were admitted to the same hospital. In both of these cases the dosage had been clearly excessive, the drug had been continued after the onset of vomiting and convulsions, and the outcome had been fatal. I have not used rectal aminophylline since and have not missed it. I would advise that its use be generally discontinued. My reasons for this recommendation are as follows:

1. Cases of aminophylline poisoning are probably more common than the literature indicated. Some deaths have undoubtedly been attributed to other causes. In other instances as in those mentioned above, publication may have been avoided because the details may have caused embarrassment to physicians, hospital or attendants, since this is usually an "iatrogenic" disease.

2. No evidence has been adduced to show that rectal aminophylline in the dosage recommended by Dr. Soifer is "usually adequate" for the treatment of asthma. Since rectal absorption is unpredictable, clinical effectiveness is probably equally uncertain.

3. Rectal administration is usually recommended for home use. It seems hazardous to relegate to the parents the responsibility for safe dosage, appropriate time intervals, and the interpretation of toxic symptoms. If the dyspnea is not relieved, parents are likely to increase the dose, shorten the interval, or add other drugs which may potentiate aminophylline toxicity. A severe asthma attack in their child is likely to upset otherwise calm and dependable parents.

4. Asthma which is adrenalin-resistant but aminophylline-responsive is not common in children but it certainly occurs. In some of these distressing cases intravenous aminophylline gives prompt relief. If, however, such a patient were given rectal aminophylline and no relief were obtained, it would be impossible to tell whether absorption had been inadequate or whether the patient was aminophylline-resistant. It would then, of course, be hazardous to give intravenous aminophylline without waiting several hours.

5. Ephedrine and related compounds orally and adrenalin by inhalation are reasonably safe and usually effective medications for home use. ACTH and corticosteroids are so effective in terminating attacks of adrenalin-resistant asthma and so relatively safe used for such brief periods that aminophylline in any form is now rarly needed in either home, office, or hospital. I believe the rectal route should now be considered obsolete.

MEINHARD ROBINOW, M.D.

On inquiry Dr. Robinow replied that the child weighed approximately 10 kilograms. The suppository was one of 3¼ grains, making a dosage of 6.25 mg. per kilogram. This is higher than the dosage recommended by Dr. Soifer to which he refers. *Editor.*

To the Editor:

O Tempora, O Mores!

Are medical meetings reduced to this!!!

An Announcement in the *New England Journal of Medicine*, Aug. 8, 1957:

AMERICAN ACADEMY OF PEDIATRICS

The twenty-sixth annual meeting of the American Academy of Pediatrics will be held at the Palmer House, Chicago, October 7 to 10, 1957. The meeting will be preceded by two days of seminars, on October 5 and 6.

On October 8 the William E. Ladd Award will be presented to Mr. Denis Browne, F.R.C.S., of London, who will deliver an address entitled "The Use of Logic in Surgery." At this annual meeting Dr. Stewart H. Clifford, of Brookline, Massachusetts, will be installed as president.

A welcome hour on Sunday, October 6, will be held by courtesy of Ross Laboratories; on Monday, October 7, a special symphony concert with Arthur Fiedler conducting will be presented by courtesy of Johnson and Johnson; breakfast on October 8 will be by courtesy of Libby's Baby Foods; the cocktail hour and floor show on October 9 will be by courtesy of Mead Johnson and Company, with floral decorations by courtesy of Pet Milk Company; luncheon for the ladies on October 7 will be by courtesy of the Carnation Company.

"A PEDIATRICIAN"

(Name withheld by request.—Ed.)

News and Notes

A separate Department of Pediatrics was established at the **University of Vermont, College of Medicine**, Burlington, July 1, 1957. Previously, pediatrics had been a division of the Department of Medicine.

The **American Academy of Pediatrics** will grant twelve or more fellowships to pediatric residents for the fiscal year 1958-1959 and covering a period of six months to one year. These fellowships have been created to enable young physicians in the United States and Canada, who are in financial need, to complete their pediatric training. The fellowships carry a stipend of $500 to $1,000 depending on the length of time required to complete training and the need. The fellowships have been made possible by a grant to the Academy from Mead Johnson & Company and will be granted as of July 1, 1958. *The deadline for receipt of applications will be March 1, 1958.*

Requirements for the awards: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by July 1, 1958, one year of pediatric residency approved by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident requesting the fellowship stating that he intends to enter pediatric private practice at the conclusion of the residency training required for certification by the American Board of Pediatrics. Consideration will be given to geographic spread of appointments, so that all sections of the country will be represented, and preference will be exhibited for well qualified but smaller training centers which perhaps have fewer resources for assisting residents in training than do some of the larger centers. Note that research interests and accomplishments and desire to enter academic pediatrics are not criteria for the awards.

Members of the Committee on Residency Fellowships of the American Academy of Pediatrics will make final decision on the granting of the awards.

Those interested in applying may correspond with the American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Illinois.

A review of clinical pediatrics will be given by the **New York University Post-Graduate Medical School** on a full-time basis from November 18 through 23, 1957, under the direction of Dr. Adolph G. De Sanctis. The course will consist of a review of the practical problems encountered in a

pediatric practice. Clinical lectures, conferences, ward rounds and case demonstrations will be given.

For further information: Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, New York.

The **Cook County Graduate School of Medicine** announces two one-week postgraduate courses in *Pediatric Cardiology*. Course I, on the Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children, by Benjamin M. Gasul, M.D., Egbert H. Fell, M.D., and associates, begins Dec. 2, 1957. Course II, on Roentgenology and Electrocardiography; Angiocardiography and Catheterization of the Heart and Great Vessels in the Diagnosis of Congenital and Acquired Malformations in the Hearts of Infants and Children, by Benjamin M. Gasul, M.D., Robert F. Dillon, M.D., and associates, begins Dec. 9, 1957.

The following announcement has recently been made by the Department of Health, Education and Welfare of the United States Public Health Service:

Thirteen months after the publication of the experimental *Bibliography of Medical Reviews, 1955*, Volume 2 made its appearance in August. In the interim, ample evidence of its acceptance was accumulated to warrant the continuation and expansion of the venture as a regular annual publication of the National Library of Medicine.

The 1,500 copies of Volume 1 were quickly distributed within the first few months and requests continued to be received right down to this writing. This time almost twice the number of copies were printed and sufficient supplies should be available from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., at 60 cents per copy.

The internal format and arrangement of the second volume remain about the same as before. Complete entries including the bibliographic reference and translation of foreign title, appear under the various subject headings derived from the *Current List of Medical Literature Subject Heading Authority List;* cross references are not restricted to those in the *Authority List* but are provided generously. The over-all size of the issue is substantially greater with about 1,800 review articles cited as compared with 1,100 articles in Volume 1. In both volumes, all material was culled exclusively from journals indexed in the *Current List of Medical Literature*. The collection basis for *Bibliography of Medical Reviews III* has been broadened to include review articles published in journals which are not already indexed in the *Current List of Medical Literature*. Consequently, the next volume will show a further increase in size as well as other format changes including the provision of an author approach to the material.

The American Foundation for Allergic Diseases announces **Post-doctoral Fellowships in Research and Clinical Allergy** for two years each. Stipend: first year, $4,500; second year, $4,750; laboratory and travel expenses for two-year period, $750.

Requirements: Candidates must be graduates of approved medical schools and must have completed one or two years of the graduate training required as a preliminary to certification by the Boards of Internal Medicine or Pediatrics; they are to divide their time between research and clinical training, and in the second year 10 or 15 per cent of a candidate's time might be devoted to teaching. The respective Institutions have taken the necessary steps to have this training credited toward the Sub-specialty in Allergy by the Board of Internal Medicine and the Board of Pediatrics.

Requests for applications should be sent directly to one of the following, in whose field the candidate would like to work: Dr. Colin M. MacLeod, Professor of Research Medicine, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce Streets, Philadelphia 4, Pa., or Dr. Herman N. Eisen, Professor of Medicine (Dermatology), Washington University School of Medicine, 600 South Kingshighway, St. Louis 10, Mo. Applications should be filed no later than Dec. 15, 1957, with any of the above.

Books

The Mentally Ill Child. A Guide for Parents. Steven B. Getz, Ph.D., and Elizabeth L. Rees, M.D. Springfield, Ill., 1957, Charles C Thomas, Publisher, 88 pages. Price $3.50.

This attempt by a psychologist and a pediatrician to prepare a guide for parents with a mentally ill young child cannot be described as a successful effort. The failure, which stands out clearly in the book, is due to the fact that sufficient material or information is lacking in regard to the management of young children with mental illness to warrant it to be put in book form. The 68 pages of text, containing considerable padding, could have been condensed into a pamphlet or brochure one-third in size. The book concerns itself with the very young child with mental illness. Fortunately, compared with other mental conditions at this age such as retardation, the incidence of mental illness is very low. Further we have no facts, only theories, as the cause. Until more is known of the etiology, the treatment and management of the distressing illness presented by these young children is largely groping in the dark. There are so many differing environmental factors involved with each individual mentally ill young child, that it is difficult if not impossible to write a "guide" for parents as to their care and management. It has seemed unfortunate to the reviewer that the term "schizophrenia" has come to be used nosologically to describe mental illness in this age group. The term connotes the "schizophrenia" of later childhood and adolescence which fills our institutions to overflowing. There is no evidence based on facts that the same etiological factors are involved in both conditions. It suggests a throwback to the Kraepelin classification period of psychiatry, an attempt to give it a name even if you do not know what it is or what causes it.

The Metabolic Response to Neonatal Surgery. Peter P. Rickham, M.S., M.D., F.R.C.S., Cambridge, 1957, Harvard University Press, 83 pages. Price, $5.00.

In this monograph Dr. Rickham discusses the metabolic changes occurring in neonates during the course of surgical procedures. Balance studies were completed in nine infants undergoing a variety of surgical conditions. These infants ranged in birth weight from 1,902 to 3,800 grams and in age from 1 day to 3 weeks. Each case is presented individually and the metabolic data are shown in clear diagrammatic fashion. In addition, the author includes discussions of the techniques of balance study, the metabolism of neonates, and the metabolic changes subsequent to surgical procedures in adults. Finally, on the basis of these studies and a large clinical experience, the author discusses the principles of preoperative and postoperative care applicable to the neonatal period.

It is of great interest that much of the metabolic data reinforces clinical impressions current in this field: namely, (a) that the infant around the time of birth has been prepared to withstand stress and tolerates major surgery with considerably more equanimity than infants over 3 weeks of age, and (b) that infants with intestinal obstruction form a unique and difficult group because vomiting and gastric suction rapidly deplete the body of water and electrolytes and prolonged ileus is a common sequel to surgery. The author presents a strong case against overtreatment with fluids, particularly with normal saline.

To all pediatricians and surgeons and to those interested in metabolic studies, this work will be a mine of information. The reviewer believes, however, that this eminently usable volume is destined to be chronically missing from libraries, and to turn up, well marked and thumbed, on the infant

surgery wards in the hands of the resident physician.

M. M. D.

Perinatal Loss in Modern Obstetrics. Robert E. L. Nesbitt, Jr., M.D., Philadelphia, 1957, F. A. Davis Co., 450 pages. Price $12.50.

This text is a lucidly written, well-organized discussion of the factors involved in the broad field of reproductive failure. Although Dr. Nesbitt is the present chairman of the Department of Obstetrics and Gynecology at Albany Medical College, the volume reflects the previous training ground of the author, the Department of Obstetrics at Johns Hopkins University. This department has traditionally been concerned with the problems of perinatal loss, neonatal morbidity, and the sequelae of perinatal disease.

This volume fills a great need summarizing, as it does, a voluminous and often controversial literature. The illustrations and bibliography are excellent. Pediatricians will welcome particularly the chapters on prematurity, anoxia, birth injury, infections, and hemolytic disease. However, since the aim of the author in "providing a reservoir of current knowledge concerning complex maternal—fetal relationships," has been amply achieved, this volume will be widely used by obstetricians, pediatricians, pathologists, anesthetists, public health workers, and all those interested in the challenging problems presented by perinatal death, and the distressing neurologic sequelae of disturbed perinatal physiology.

—M. D.

Blindness in Children. Miriam Norris, Patricia J. Spaulding, and Fern H. Brodie, Chicago, 1957, University of Chicago Press.

This is one book that every physician should read. Most pediatricians have at least one visually handicapped child under their supervision who is capable of normal physical and intellectual development. But few have a clear concept of the child's needs and how they can help provide the essential professional skills and services needed to encourage normal development. This book provides that concept.

The authors, from the University of Chicago Clinics, made a longitudinal study of 295 blind children, beginning as soon after birth as the diagnosis was made. Sixty-six were studied intensively with repeated psychological testing, home visits, nursery school supervision, and guidance for parents. The first part of the book takes up the material studied, the psychological tests used, and the analysis of data. The last half of the book presents six case histories which everyone should read. With these case histories they not only illustrate their method of study and conclusions, but they also give the reader an insight into the handicap (or rather lack of handicap) of blindness. With this study the authors have confirmed the long-held idea that blind children in the preschool years require no special training but that, if loved and allowed to develop as a normal child would, they will grow up in a normal way and compete with their sighted companions in every sphere.

Epilepsy. Letitia Fairfield, M.D., New York, 1957, Philosophical Library Inc., 159 pages. Price $4.75.

In the book entitled *Epilepsy* by the British author, Dr. Letitia Fairfield, special emphasis has been placed on the social outlet for the epileptic patient, and the various community and governmental organizations which exist for this purpose are described. Of particular interest for the non-British reader will probably be Chapter six, in which the author discusses "colonies" for patients with epilepsy. These colonies are excellent places where the epileptic patient may receive medical care and training for a trade, after which he is discharged from the institution, equipped to be self-sufficient. The first colony of this type was established in 1888. Since that time, other colonies have been established for this purpose. These arrangements apparently have given excellent results, and such an approach to the patient with epilepsy is a practical one.

D. C.

Liver: Structure and Function. Hans Popper, M.D., and Fenton Schaffner, M.D., New York, 1957, McGraw-Hill Book Co., 777 pages. Price $20.00.

As the title implies, this book correlates hepatic structure with function. Both gross and microscopic structure is described, with and excellent discussion of physiologic and biochemical functions. All phases of liver disease are covered. Liver function tests are discussed.

The book is divided into seven parts. The first deals with normal structure and function, the second with pathologic phenomena in the hepatobiliary system, the third with the clinical study of hepatic function and structure, the fourth with diffuse diseases of the liver, the fifth with focal diseases of the liver, the sixth with tumors of the liver and biliary tree, and the seventh with internal and external environment of the liver.

This book should be an excellent reference for both the clinician and the pathologist.

H. W.

A Synopsis of Children's Diseases, ed. 2. John Rendle-Short, M.B., M.R.C.P., Bristol, 1957, John Wright & Sons Ltd., 624 pages.

The place and value of a "Synopsis" is debatable. As a group their use and publication have been decreasing in recent years. As the author states, "It should not take the place of standard text-books." He also adds in the preface to the first edition that it "will be of value to those preparing for examinations." Leaving this aside, it can be added that the Rendle-Short pediatric synopsis is excellent of its kind, and "tops" in pediatrics. The author has an unusual facility of summing up the essential knowledge of a condition or a disease and its treatment in a few words. The first edition was published only three years ago and hence it obviously has made a place for itself. It is somewhat revised to bring in the advances of the last three years.

Pediatric Dentistry. M. Michael Cohen, D.M.D., St. Louis, 1957, The C. V. Mosby Company, 607 pages. Price $14.75.

Pedodontics has become an important subspeciality of dentistry in recent years, even having its own "American Board." While this text is directed to the dental profession, pediatricians will find much of interest in the book. Dr. Cohen has had an extensive experience as stomatologist to the Boston Floating Hospital, and some sixteen collaborators have written chapters on fields such as orthodontics, in which they are regarded as authorities. An excellent chapter on the "Physical Growth and the Development of the Child" is contributed by Drs. Kreidberg and Baty of the pediatric department of the Tufts University School of Medicine.

The Premature Baby, ed. 4. V. Mary Crosse, M.D., Boston, 1957, Little, Brown & Company, 242 pages.

An extensively revised edition of Dr. Crosse's well-known text on the premature infant, first published in 1945. The discussion of the care of the premature infant is explicit and based on her many years of experience in charge of the premature unit of the Sorrento Maternity Hospital in Birmingham, England. The statistical data has been revised into three periods, bringing it up to 1955. It is a most satisfactory and practical discussion of the problems of the premature infant.

Editor's Column

THE IMPORTANCE OF ATTITUDES

OUR thoughts recently went back to the late C. Anderson Aldrich —one of the finest pediatricians of our generation—who a number of years ago became convinced that a child's development was largely determined by the "attitudes" of those making up his environment. We recall his saying many times in off-record discussions, "We should teach attitudes, and not a mass of specific details as to the feeding and care of the infant and child." This was at a time when rigidity was dogmatically emphasized in the many books published for parental guidance. His philosophy culminated in that pediatric classic, *Babies Are Human Beings,* published in 1942.

The occasion was the reading of a brochure recently published by the University of Wisconsin Press, *A Word to Parents About Mental Hygiene,** containing three talks in the Knapp lecture series at the University by Dr. Leo Kanner, professor of Child Psychiatry and Director of the Children's Psychiatric Service at Johns Hopkins. Dr. Kanner's theme is that the child's development toward normal or abnormal mental health, his behavior, and his adjustment to life are largely determined by the attitudes of those—chiefly parents—surrounding him in his early years. It was interesting to find one of the leading child psychiatrists stressing today the same viewpoint stressed by a pediatric leader over twenty years ago.

While the three essays in the brochure are addressed to parents, the pediatrician will find them profitable and worthwhile reading. Dr. Kanner traces the development of psychiatry through three major stages: a formal, an epithetic, and a thematic in which behavior is regarded as deriving its existence, its form, and its meaning from the totality of its setting. Attitudes are not something casual or fortuitous but are shaped by the totality of experiences which go into the making of personality. So far as the child is concerned, an environment in which the parental attitudes are those of acceptance, affection, and approval promises a good healthy emotional adjustment. The writing is clear, reflecting clear thinking, and free from what the author terms the "obscuring pseudo-professional clichés" which have muddled much of the writings of the child psychiatrists.

*University of Wisconsin Press, Madison, Wisconsin. Price (Paper) $1.00.